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=> d his

     (FILE 'REGISTRY' ENTERED AT 11:45:30 ON 13 AUG 2001)
                DEL HIS Y
                E AMVERMECTIN/CN
                E AVERMECTIN/CN
L1            1 S E3
                E MILBEMYCIN/CN
L2            1 S E3
                E SCAN
                E DORAMECTIN/CN
L3            1 S E3

     FILE 'HCAPLUS' ENTERED AT 11:48:24 ON 13 AUG 2001
L4         1469 S L1 OR L2 OR L3  OR MILBEMYCIN# OR AVERMECTIN# OR DORAMECTIN#
L5        69279 S IMPLANT?
L6            7 S L4 AND L5
L7       108715 S IMPLANT?/AB
L8            7 S L4 AND L7
L9           10 S L8 OR L6
L10       22414 S (CONTROL? OR SUSTAIN? ) (L) RELEAS?
L11          14 S L10 AND L4
L12       49063 S DRUG DELIVERY SYSTEM#
L13          49 S L4 AND L12
L14          23 S L13 AND (CATTLE# OR SHEEP OR LIVESTOCK? OR ANIMAL#)
L15        8198 S EAR#
L16           2 S L15 AND L4

     FILE 'REGISTRY' ENTERED AT 11:57:19 ON 13 AUG 2001
                E LACTOSE/CN
L17           1 S E3
                E MAGNESIUM STEARATE/CN
L18           1 S E3
                E SODIUM STARCH GLYCOLATE/CN
L19           1 S E3
                E  BMT/CN
                E BUTYLATED HYDROXYTOLUENE/CN
L20           1 S E3
                E BUTYLATED HYDROXYANISOLE/CN
L21           1 S E3
                E POLYVINYL PYRROLIDONE/CN
L22           0 S E3
                E POLYVINYLPYRROLIDONE/CN
L23           1 S E3

     FILE 'HCAPLUS' ENTERED AT 11:59:19 ON 13 AUG 2001
L24       16335 S LACTOSE OR BULKING AGENT#
L25        3628 S L18 OR MAGNESIUM STEARATE
L26         777 S L19 OR SODIUM STARCH GLYCOLATE
L27       21094 S BUTYLATED HYDROXYTOLUENE OR BUTYLATED HYDROXYANISOLE OR L21
O
L28           8 S L4 AND (L24 OR L25 OR L26 OR L27)
L29           5 S L28 AND (L5 OR L10 OR L12)
L30          21 S L9 OR L11
L31          22 S L16 OR L30
L32          20 S L31 NOT L29
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     FILE 'USPATFULL' ENTERED AT 12:03:56 ON 13 AUG 2001
L33          103 S L1 OR L2 OR L3
L34        85115 S  IMPLANT?
L35           33 S L33 AND L34
L36          245 S (AVERMECTIN# OR DORAMECTIN# OR MILBEMYCIN#)/TI,AB,CLM
L37          270 S L36 OR L33
L38           60 S L37 AND L34
L39           60 S L38 AND (CATTLE OR LIVESTOCK# OR SHEEP# OR ANIMAL#)
L40           35 S L38 AND (CATTLE OR LIVESTOCK# OR SHEEP# OR
ANIMAL#)/TI,CLM,AB

     FILE 'HCAPLUS, USPATFULL' ENTERED AT 12:06:45 ON 13 AUG 2001
L41           60 DUP REM L29 L32 L40 (0 DUPLICATES REMOVED)

     FILE 'USPATFULL' ENTERED AT 12:07:21 ON 13 AUG 2001
L42            6 S L40 AND EAR#
L43        55967 S L17 OR LACTOSE
L44        42199 S L18 OR MAGNESIUM STEARATE
L45         1591 S L19 OR SODIUM STARCH GLYCOLATE
L46         3525 S BUTYLATED HYDROXYANISOLE OR HYDROXYTOLULENE OR HYDROXY (W)
(A
L47         3158 S BUTYLATED (W) (HYDROXYANISOLE OR HYDROXYTOLULENE OR HYDROXY
(
L48         7174 S L21 OR L23 OR L47
L49         4138 S L20 OR L21 OR L47
L50        40509 S L23 OR POLYVINYLPYRROLIDONE OR POLYVINYL PYRROLIDONE
L51          176 S L50 AND L49 AND L45 AND L44 AND L43
L52            0 S L51 AND L37
L53           35 S L41
L54           29 S L41 AND (L50 OR L49 OR L45 OR L44 OR L43)
L55           29 S L40 AND (L50 OR L49 OR L45 OR L44 OR L43)
L56           25 S L55 NOT L42
L57        28004 S IMPLANT?/AB,TI,CLM
L58            0 S L56 AND L57
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=> fil hcaplus

FILE 'HCAPLUS' ENTERED AT 12:17:01 ON 13 AUG 2001
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2001 AMERICAN CHEMICAL SOCIETY (ACS)
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FILE COVERS 1947 - 13 Aug 2001  VOL 135 ISS 8
FILE LAST UPDATED: 12 Aug 2001  (20010812/ED)

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

 This file supports REGistRY for direct browsing and searching of
 all substance data from the REGISTRY file.  Enter HELP FIRST for
 more information.

HCAplus now provides online access to patents and literature covered
in CA from 1947 to the present.  On April 22, 2001, bibliographic
information and abstracts were added for over 2.2 million references
published in CA from 1947 to 1966.

'OBI' IS DEFAULT SEARCH FIELD FOR 'HCAPLUS' FILE

=> d his l1-l32


     (FILE 'REGISTRY' ENTERED AT 11:45:30 ON 13 AUG 2001)
               DEL HIS Y
               E AMVERMECTIN/CN
               E AVERMECTIN/CN
L1           1 S E3
               E MILBEMYCIN/CN
L2           1 S E3
               E SCAN
               E DORAMECTIN/CN
L3           1 S E3

     FILE 'HCAPLUS' ENTERED AT 11:48:24 ON 13 AUG 2001
L4        1469 S L1 OR L2 OR L3  OR MILBEMYCIN# OR AVERMECTIN# OR DORAMECTIN#
L5       69279 S IMPLANT?
L6           7 S L4 AND L5
L7      108715 S IMPLANT?/AB
L8           7 S L4 AND L7
L9          10 S L8 OR L6
L10      22414 S (CONTROL? OR SUSTAIN? ) (L) RELEAS?
L11         14 S L10 AND L4
L12      49063 S DRUG DELIVERY SYSTEM#
L13         49 S L4 AND L12
L14         23 S L13 AND (CATTLE# OR SHEEP OR LIVESTOCK? OR ANIMAL#)
```

```
L15         8198 S EAR#
L16            2 S L15 AND L4

     FILE 'REGISTRY' ENTERED AT 11:57:19 ON 13 AUG 2001
                  E LACTOSE/CN
L17             1 S E3
                  E MAGNESIUM STEARATE/CN
L18             1 S E3
                  E SODIUM STARCH GLYCOLATE/CN
L19             1 S E3
                  E  BMT/CN
                  E BUTYLATED HYDROXYTOLUENE/CN
L20             1 S E3
                  E BUTYLATED HYDROXYANISOLE/CN
L21             1 S E3
                  E POLYVINYL PYRROLIDONE/CN
L22             0 S E3
                  E POLYVINYLPYRROLIDONE/CN
L23             1 S E3

     FILE 'HCAPLUS' ENTERED AT 11:59:19 ON 13 AUG 2001
L24         16335 S LACTOSE OR BULKING AGENT#
L25          3628 S L18 OR MAGNESIUM STEARATE
L26           777 S L19 OR SODIUM STARCH GLYCOLATE
L27         21094 S BUTYLATED HYDROXYTOLUENE OR BUTYLATED HYDROXYANISOLE OR L21
O
L28             8 S L4 AND (L24 OR L25 OR L26 OR L27)
L29             5 S L28 AND (L5 OR L10 OR L12)
L30            21 S L9 OR L11
L31            22 S L16 OR L30
L32            20 S L31 NOT L29

=> d .ca hitstr l29 1-5;d .ca hitstr l32 1-20


L29  ANSWER 1 OF 5  HCAPLUS  COPYRIGHT 2001 ACS
ACCESSION NUMBER:        2001:396647  HCAPLUS
DOCUMENT NUMBER:         135:10020
TITLE:                   Preparation of controlled release
                         of active ingredients
INVENTOR(S):             Huron, Sebastien; Lacoste, Eric
PATENT ASSIGNEE(S):      Akzo Nobel N.V., Neth.
SOURCE:                  PCT Int. Appl., 26 pp.
                         CODEN: PIXXD2
DOCUMENT TYPE:           Patent
LANGUAGE:                English
FAMILY ACC. NUM. COUNT:  1
PATENT INFORMATION:

     PATENT NO.        KIND  DATE          APPLICATION NO.   DATE
     ---------------   ----  --------      ---------------   --------
     WO 2001037811      A1   20010531      WO 1999-EP8979    19991122
         W:  AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU,
             CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL,
             IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA,
             MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI,
             SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM,
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AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

AB A new compn. is disclosed which is esp. designed for combating external and internal parasites. In one embodiment, this compn. contains, as an active ingredient, an endectocide, the form of a s.c. implant constituted by 1 or more pellets that release the active ingredient in a predetd. and controlled way. In specific embodiments, the endectocide is an avermectin or a milbemycin, in particular ivermectin. Thus, pellets contained ivermectin 136.0, Polyox 301 20.0, lactose 42.0, talc 8.0, Mg stearate 2.0, and Et cellulose 2.0 g.

IC ICM A61K009-20
ICS A61K009-00; A61P033-00

CC 63-6 (Pharmaceuticals)

ST **controlled release avermectin** pellet;
implant controlled release avermectin

IT Polyoxyalkylenes, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(alkyl ethers; prepn. of **controlled release** of active ingredients)

IT **Drug delivery systems**
(**controlled-release**; prepn. of **controlled release** of active ingredients)

IT **Drug delivery systems**
(**implants, controlled-release**; prepn. of **controlled release** of active ingredients)

IT **Drug delivery systems**
(pellets, **controlled-release**; prepn. of **controlled release** of active ingredients)

IT Antibiotics
Antitumor agents
Gelation agents
Parasiticides
Vaccines
(prepn. of **controlled release** of active ingredients)

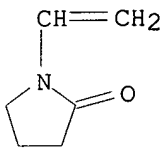
IT Alditols
Carbohydrates, biological studies
Disaccharides
Growth promoters, animal
Hormones, animal, biological studies
Polyoxyalkylenes, biological studies
Vitamins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prepn. of **controlled release** of active ingredients)

IT 63-42-3, **Lactose** 7631-86-9, Silica, biological studies
9000-69-5, Pectin 9002-89-5, Poly(vinyl alcohol) **9003-39-8**, PVP 9004-34-6D, Cellulose, derivs. 9004-57-3, Ethyl cellulose 9005-25-8D, Starch, derivs. 25322-68-3, Polyethylene glycol 25322-68-3D, Polyethylene glycol, alkyl ethers **51570-36-6**, **Milbemycin** 70288-86-7, Ivermectin 71751-41-2, Abamectin **73989-17-0**, **Avermectin**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prepn. of **controlled release** of active

ingredients)
IT **9003-39-8**, PVP **51570-36-6, Milbemycin**
73989-17-0, Avermectin
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prepn. of **controlled release** of active
ingredients)
RN 9003-39-8 HCAPLUS
CN 2-Pyrrolidinone, 1-ethenyl-, homopolymer (9CI) (CA INDEX NAME)

CM 1

CRN 88-12-0
CMF C6 H9 N O



RN 51570-36-6 HCAPLUS
CN Milbemycin (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 73989-17-0 HCAPLUS
CN Avermectin (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
REFERENCE COUNT: 6
REFERENCE(S): (1) Boehringer Ingelheim Kg; DE 4230563 A 1994
HCAPLUS
(2) Chih-Ming, C; US 5458887 A 1995 HCAPLUS
(3) Chih-Ming, C; US 5472708 A 1995 HCAPLUS
(4) Haessle Ab; WO 8702240 A 1987 HCAPLUS
(5) Huatan, H; WO 9915166 A 1999 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L29 ANSWER 2 OF 5 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:372056 HCAPLUS
DOCUMENT NUMBER: 131:23523
TITLE: Long acting injectable formulations containing hydrogenated castor oil
INVENTOR(S): Williams, James B.; Chern, Rey T.
PATENT ASSIGNEE(S): Merck & Co., Inc., USA; Merial LLC
SOURCE: PCT Int. Appl., 30 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9927906	A1	19990610	WO 1998-US19016	19980914

W: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GE, HR,

HU, ID, IL, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TJ, TM, TR, TT, UA, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

ZA 9810975	A	19990603	ZA 1998-10975	19980201	
AU 9893858	A1	19990616	AU 1998-93858	19980914	
EP 1035835	A1	20000920	EP 1998-946961	19980914	
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, SI, FI, RO					
BR 9815352	A	20001017	BR 1998-15352	19980914	
US 6174540	B1	20010116	US 1998-152775	19980914	
NO 2000002830	A	20000803	NO 2000-2830	20000602	

PRIORITY APPLN. INFO.:

US 1997-67374	P	19971203
GB 1998-9792	A	19980507
WO 1998-US19016	W	19980914

AB This invention relates to novel, long-acting injectable formulations. These formulations comprise: (a) a therapeutic agent selected from the group consisting of, e.g., insecticides, acaricides, parasiticides, growth enhancers and oil-sol. NASIDS; (b) hydrogenated castor oil and (c) a hydrophobic carrier comprising: (i) triacetin, benzyl benzoate or Et oleate or a combination thereof; and (ii) acylated monoglycerides, Pr dicaprylates/dicaprates or caprylic/capric acid triglycerides or a combination thereof. Also provided is a method for the treatment or prevention of various disease states by the parental administration of the invention formulations. A compn. was prepd. contg. ivermectin 17.6, n-Pr gallate 0.10, Thixcin R 5.0, triacetin 200, and Myvacet 9-45 qs to 500g.

IC ICM A61K009-08
ICS A61K047-14; A61K047-44; A61K031-70; A61K031-365

CC 63-6 (Pharmaceuticals)

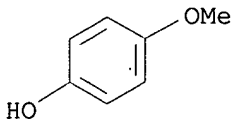
IT **Drug delivery systems**
(injections; long acting injectable formulations contg. hydrogenated castor oil)

IT 121-79-9, Propyl gallate 128-37-0, Bht, biological studies **25013-16-5**, Bha 38098-46-3, Monothioglycerol
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antioxidant; long acting injectable formulations contg. hydrogenated castor oil)

IT 50-33-9, Phenylbutazone, biological studies 22071-15-4, Ketoprofen 22204-53-1, Naproxen 35367-38-5, Diflubenzuron 38677-85-9, Flunixin 40596-69-8, Methoprene **51570-36-6**, **Milbemycin** 53716-49-7, Carprofen 66215-27-8, Cyromazine 71125-38-7, Meloxicam 71751-41-2, Abamectin 72490-01-8, Phenoxycarb **73989-17-0**, **Avermectin** 95737-68-1, Pyriproxyfen 103055-07-8, Lufenuron 113507-06-5, Moxidectin **117704-25-3**, **Doramectin** 119791-41-2, Emamectin 120068-37-3, Fipronil 123997-26-2, Eprinomectin 138261-41-3, Imidacloprid 163120-03-4 163120-03-4D, derivs.
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(long acting injectable formulations contg. hydrogenated castor oil)

IT **25013-16-5**, Bha
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(antioxidant; long acting injectable formulations contg. hydrogenated castor oil)
RN 25013-16-5 HCAPLUS
CN Phenol, (1,1-dimethylethyl)-4-methoxy- (9CI) (CA INDEX NAME)



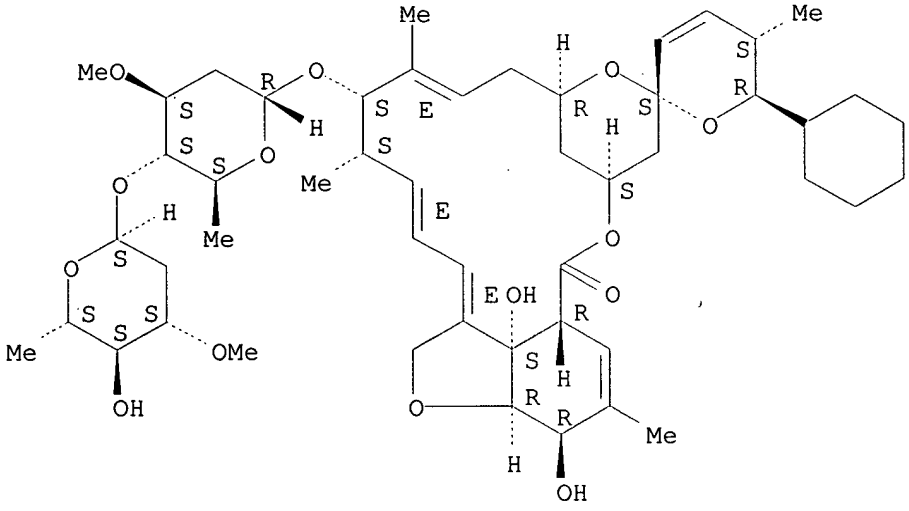
D1—Bu-t

IT **51570-36-6, Milbemycin 73989-17-0, Avermectin 117704-25-3, Doramectin**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(long acting injectable formulations contg. hydrogenated castor oil)
RN 51570-36-6 HCAPLUS
CN Milbemycin (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 73989-17-0 HCAPLUS
CN Avermectin (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 117704-25-3 HCAPLUS
CN Avermectin A1a, 25-cyclohexyl-5-O-demethyl-25-de(1-methylpropyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



REFERENCE COUNT: 7
REFERENCE(S): (1) Ashmont Holdings Ltd; WO 9711709 A 1997 HCAPLUS

(2) Bayer AG; DE 19613972 A 1997 HCAPLUS
(3) Itil, T; US 4330538 A 1982 HCAPLUS
(4) Merck & Co Inc; EP 0535734 A 1993 HCAPLUS
(5) Merck & Co Inc; EP 0413538 A 1991 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L29 ANSWER 3 OF 5 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:231498 HCAPLUS
DOCUMENT NUMBER: 130:257359
TITLE: Parasiticidal formulations of **avermectins** or **milbemycins**
INVENTOR(S): Huatan, Hiep
PATENT ASSIGNEE(S): Pfizer Limited, UK; Pfizer Inc.
SOURCE: PCT Int. Appl., 19 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9915166	A1	19990401	WO 1998-EP5720	19980904
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9897422	A1	19990412	AU 1998-97422	19980904
EP 1014970	A1	20000705	EP 1998-951367	19980904
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
BR 9812385	A	20000912	BR 1998-12385	19980904

PRIORITY APPLN. INFO.:
GB 1997-20228 A 19970923
GB 1998-10143 A 19980512
WO 1998-EP5720 W 19980904

AB The invention provides a solid implant comprising at least one parasiticidal compd. having low aq. soly. and tableting excipients including a bulking agent. Implants according to the invention are convenient to administer and provide prolonged protection against parasites in cattle and sheep. Implants contg. doramectin 40, .beta.-anhyd. lactose 52, Explotab 5, and Mg stearate 3% by wt. were prepd. and implanted into 16 cows at a dose of 500 .mu.g/kg. In each case single case-host tick activity was obtained for > 50 days, and control of helminths was obtained for .apprx. 90 days.

IC ICM A61K031-35
ICS A61K031-365; A61K009-00; A61K009-20

CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 1

ST **avermectin milbemycin sustained release implant** parasiticide

IT Ear
(**implants** for; **sustained-release**

implant formulations of parasiticides **avermectins** or **milbemycins**)

IT **Sustained release drug delivery systems**
(**implants**, s.c.; **sustained-release implant** formulations of parasiticides **avermectins** or **milbemycins**)

IT **Implants** (**drug delivery systems**)
(**sustained release**, s.c.; **sustained-release implant** formulations of parasiticides **avermectins** or **milbemycins**)

IT Anthelmintics
Antioxidants (pharmaceutical)
Cattle
Mite and Tick
Parasiticides
Radiation sterilization (cleaning)
Reducing agents
Sheep
Sterilization (cleaning)
(**sustained-release implant** formulations of parasiticides **avermectins** or **milbemycins**)

IT **51570-36-6, Milbemycin 73989-17-0, Avermectin 117704-25-3, Doramectin**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**sustained-release implant** formulations of parasiticides **avermectins** or **milbemycins**)

IT 128-37-0, **Butylated hydroxytoluene**, biological studies **557-04-0, Magnesium stearate** 5965-66-2, .beta.-**Lactose 9003-39-8**, Polyvinyl pyrrolidone **9063-38-1**, Explotab **25013-16-5, Butylated hydroxyanisole**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**sustained-release implant** formulations of parasiticides **avermectins** or **milbemycins**)

IT **51570-36-6, Milbemycin 73989-17-0, Avermectin 117704-25-3, Doramectin**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**sustained-release implant** formulations of parasiticides **avermectins** or **milbemycins**)

RN 51570-36-6 HCAPLUS
CN Milbemycin (9CI) (CA INDEX NAME)

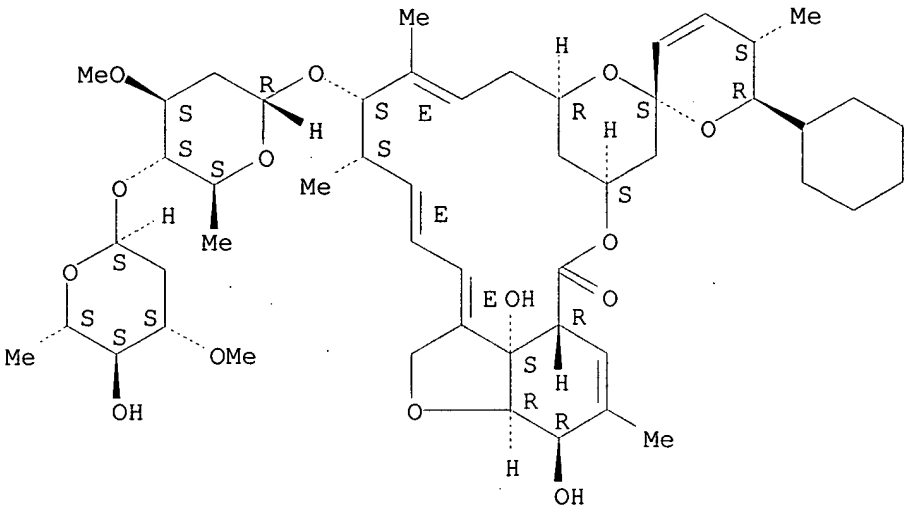
*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

RN 73989-17-0 HCAPLUS
CN Avermectin (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

RN 117704-25-3 HCAPLUS
CN Avermectin A1a, 25-cyclohexyl-5-O-demethyl-25-de(1-methylpropyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



IT **557-04-0, Magnesium stearate 9003-39-8**
, Polyvinyl pyrrolidone **9063-38-1**, Explotab **25013-16-5**
, **Butylated hydroxyanisole**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**sustained-release implant** formulations
of parasiticides **avermectins** or **milbemycins**)
RN 557-04-0 HCAPLUS
CN Octadecanoic acid, magnesium salt (9CI) (CA INDEX NAME)

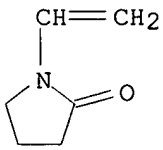
$HO_2C-(CH_2)_{16}-Me$

● 1/2 Mg

RN 9003-39-8 HCAPLUS
CN 2-Pyrrolidinone, 1-ethenyl-, homopolymer (9CI) (CA INDEX NAME)

CM 1

CRN 88-12-0
CMF C6 H9 N O



RN 9063-38-1 HCAPLUS
CN Starch, carboxymethyl ether, sodium salt (9CI) (CA INDEX NAME)

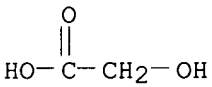
CM 1

CRN 9005-25-8
CMF Unspecified
CCI MAN

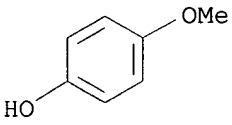
*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 79-14-1
CMF C2 H4 O3



RN 25013-16-5 HCAPLUS
CN Phenol, (1,1-dimethylethyl)-4-methoxy- (9CI) (CA INDEX NAME)



D1—Bu-t

REFERENCE COUNT: 4
REFERENCE(S): (1) Merck; EP 0240274 A 1987 HCAPLUS
(2) Merck; EP 0311195 A 1989
(3) Merck; EP 0473223 A 1992 HCAPLUS
(4) Merck; EP 0537998 A 1993 HCAPLUS

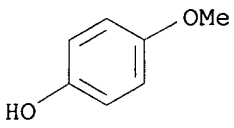
L29 ANSWER 4 OF 5 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:251809 HCAPLUS
DOCUMENT NUMBER: 128:248574
TITLE: Non-aqueous oral-drench compositions containing **avermectin** compounds
INVENTOR(S): Furstenau, Kai-Uwe
PATENT ASSIGNEE(S): Pfizer Inc., USA
SOURCE: Can. Pat. Appl., 12 pp.
CODEN: CPXXEB
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CA 2202707	AA	19971017	CA 1997-2202707	19970415
AU 9716567	A1	19971023	AU 1997-16567	19970326
AU 709310	B2	19990826		

US 5756474 A 19980526 US 1997-835454 19970408
PRIORITY APPLN. INFO.: AU 1996-9333 19960417
AB A novel non-aq. oral-drench compn. comprise from 0.01% to 2.0% (w/v) of an avermectin compd.; from 30% to 45% (wt./wt.) of an oil, said oil being selected from the group consisting of corn oil, sunflower oil, peanut oil and safflower oil; from 0.01% to 1.0% (w/v) of an oil-sol. antioxidant; and from 50% to 70% (wt./wt.) of a fatty acid ester, said fatty acid ester being selected from the group consisting of caprylic/capric triglyceride, octyl palmitate and propylene glycol dicaprylate/dicaprate. The invention is further directed to methods of using the non-aq. compn. to treat parasitic diseases in mammals. A pharmaceutical compn. contained doramectin 0.1, BHA 0.5, octyl palmitate 40, caprylic/capric triglyceride 20, and corn oil q.s. 100%.
IC ICM A61K031-71
ICS A61K047-14; A61K047-44
CC 63-6 (Pharmaceuticals)
ST oral drench pharmaceutical **avermectin** compd
IT Glycerides, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(C8-10; non-aq. oral-drench compns. contg. **avermectin** compds.)
IT Liquid dosage forms (**drug delivery systems**)
(drench; non-aq. oral-drench compns. contg. **avermectin** compds.)
IT Antioxidants
Cattle
Parasiticides
Sheep
(non-aq. oral-drench compns. contg. **avermectin** compds.)
IT Corn oil
Fatty acid esters
Peanut oil
Safflower oil
Sunflower oil
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(non-aq. oral-drench compns. contg. **avermectin** compds.)
IT **73989-17-0, Avermectin**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(non-aq. oral-drench compns. contg. **avermectin** compds.)
IT 57-55-6D, Propylene glycol, dicaprylate and dicaprate derivs. 128-37-0, Bht, biological studies 334-48-5, Capric acid 16958-85-3, Octyl palmitate **25013-16-5**, Bha 77466-09-2, Miglyol 840 **117704-25-3, Doramectin**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(non-aq. oral-drench compns. contg. **avermectin** compds.)
IT **73989-17-0, Avermectin**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(non-aq. oral-drench compns. contg. **avermectin** compds.)
RN 73989-17-0 HCAPLUS
CN Avermectin (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

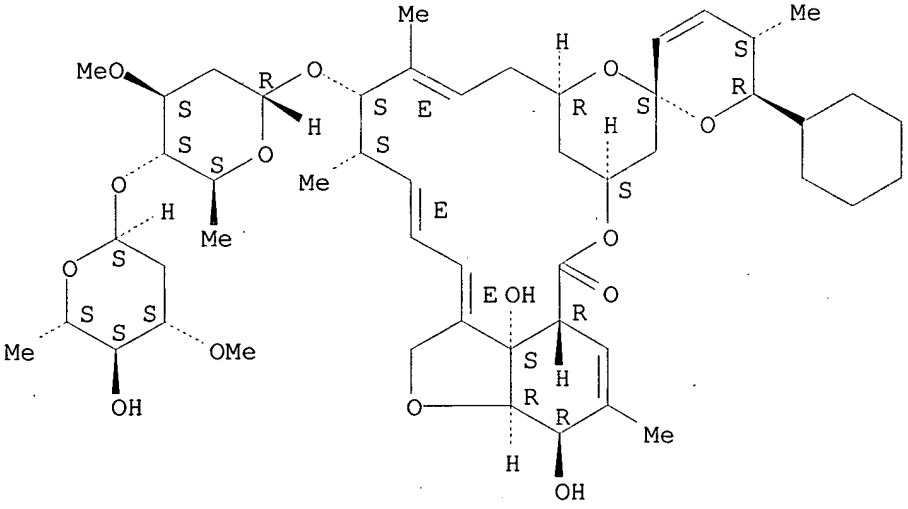
IT **25013-16-5**, Bha **117704-25-3**, **Doramectin**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(non-aq. oral-drench compns. contg. **avermectin** compds.)
RN 25013-16-5 HCAPLUS
CN Phenol, (1,1-dimethylethyl)-4-methoxy- (9CI) (CA INDEX NAME)



D1—Bu-t

RN 117704-25-3 HCAPLUS
CN Avermectin A1a, 25-cyclohexyl-5-O-demethyl-25-de(1-methylpropyl)- (9CI)
(CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L29 ANSWER 5 OF 5 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1997:513566 HCAPLUS
DOCUMENT NUMBER: 127:181167
TITLE: **Avermectin** formulation
INVENTOR(S): Komer, Gene
PATENT ASSIGNEE(S): Komer, Gene, USA
SOURCE: PCT Int. Appl., 14 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9726895	A1	19970731	WO 1997-US1361	19970128
W: AU, BR, CA, GB, MX, NZ				
US 5773422	A	19980630	US 1996-593075	19960129
CA 2244843	AA	19970731	CA 1997-2244843	19970128
AU 9717568	A1	19970820	AU 1997-17568	19970128
AU 718389	B2	20000413		
GB 2326093	A1	19981216	GB 1998-16510	19970128
GB 2326093	B2	19990922		

PRIORITY APPLN. INFO.: US 1996-593075 19960129
WO 1997-US1361 19970128

AB Novel formulations are disclosed for the administration of an avermectin, based upon the use of N-methylpyrrolidone or 2-pyrrolidone or mixts. thereof to dissolve avermectin. Formulations can contain from 0.1 % to 40 % by wt. dissolved in at least 5 % by vol. of N-methylpyrrolidone, 2-pyrrolidone or mixt. thereof. Various formulations are suitable for administration by i.m. or s.c. injection, by topical application, stomach intubation, oral and drench administration. An injection contains ivermectin 0.10-40, N-methylpyrrolidone 5-100, propylene glycol 90-0, and water 30-0%.

IC ICM A61K031-70

CC 63-6 (Pharmaceuticals)

ST **avermectin** formulation

IT Injections (**drug delivery systems**)
Solubilizers
Topical **drug delivery systems**
(**avermectin** formulation)

IT Polyoxyalkylenes, biological studies
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**avermectin** formulation)

IT Polyoxyalkylenes, biological studies
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(fatty acid esters; **avermectin** formulation)

IT 57-55-6, Propylene glycol, biological studies 94-13-3, Propylparaben 100-51-6, Benzyl alcohol, biological studies 616-45-5, 2-Pyrrolidone 872-50-4, N-Methylpyrrolidone, biological studies 3844-45-9, FD and C Blue No. 1 **9003-39-8**, Pvp 25322-68-3, Peg 25322-68-3D, fatty acid esters 60200-06-8, Clorsulon
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**avermectin** formulation)

IT 70288-86-7, Ivermectin **73989-17-0, Avermectin**
RL: PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(**avermectin** formulation)

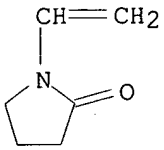
IT **9003-39-8**, Pvp
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**avermectin** formulation)

RN 9003-39-8 HCAPLUS

CN 2-Pyrrolidinone, 1-ethenyl-, homopolymer (9CI) (CA INDEX NAME)

CM 1

CRN 88-12-0
CMF C6 H9 N O



IT **73989-17-0, Avermectin**
RL: PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(**avermectin** formulation)
RN 73989-17-0 HCAPLUS
CN Avermectin (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L32 ANSWER 1 OF 20 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2001:397826 HCAPLUS
DOCUMENT NUMBER: 135:532
TITLE: Treating or preventing the early stages of degeneration of articular cartilage or subchondral bone in mammals using carprofen and derivatives
INVENTOR(S): Evans, Nigel A.; Kilroy, Carolyn R.; Lundy, Kristin M.; Pelletier, Jean-Pierre
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 24 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2001002401	A1	20010531	US 1999-283993	19990401

OTHER SOURCE(S): MARPAT 135:532
AB Treating or preventing the early stages of degeneration of articular cartilage or subchondral bone in the affected joint of a mammal is accomplished by administering a chondroprotective compd. I [R2 = (C(X)(Y))nC(O)A; A = OH, C1-4 alkoxy, amino, hydroxyamino, mono-(C1-2)alkylamino, di-(C1-2)alkylamino; X, Y = H, C1-2 alkyl; n = 1, 2; R6 = halo, C1-3 alkyl, CF3, nitro; R9 = H, C1-2 alkyl, Ph, phenyl-(C1-2)alkyl, (where Ph is optionally mono-substituted by F or Cl), -C(O)R (R = C1-2 alkyl, Ph, optionally mono-substituted by F or Cl), -C(O)OR' (R' = C1-2 alkyl)]. This treatment ameliorates, diminishes, actively treats, reverses or prevents any injury, damage or loss of articular cartilage or subchondral bone subsequent to said early stage of the degeneration. Whether or not a mammal needs such treatment is detd.

by whether or not it exhibits a statistically significant deviation from normal std. values in synovial fluid or membrane from the affected joint, with respect to at least five of the following substances: increased interleukin-1.beta.; increased tumor necrosis factor .alpha.; increased ratio of IL-1.beta. to IL-1 receptor antagonist protein; increased expression of p55 TNF receptors; increased interleukin-6; increased leukemia inhibitory factor; decreased insulin-like growth factor-1; decreased transforming growth factor .beta.; decreased platelet-derived growth factor; decreased basic fibroblast growth factor; increased keratan sulfate; increased stromelysin; increased ratio of stromelysin to tissue inhibitor of metalloproteases; increased osteocalcin; increased alk. phosphatase; increased cAMP responsive to hormone challenge; increased urokinase plasminogen activator; increased cartilage oligomeric matrix protein; and increased collagenase.

IC ICM A61K031-47
ICS A61K031-40
NCL 514412000
CC 1-12 (Pharmacology)
IT Drug delivery systems
(tablets, **sustained-release**; carprofen and derivs. for treatment or prevention of early stages of degeneration of articular cartilage or subchondral bone)
IT 50-02-2, Dexamethasone 52-67-5, Penicillamine 57-22-7, Vincristine 57-66-9, Probenecid 57-96-5, Sulfinpyrazone 59-05-2, Methotrexate 64-86-8, Colchicine 118-42-3, Hydroxychloroquine 315-30-0, Allopurinol 446-86-6, Azathioprine 564-25-0, Doxycycline 865-21-4, Vinblastine 3416-24-8, Glucosamine 3562-84-3, Benzbromarone 7440-57-5D, Gold, aurothio group-contg. compds. 9004-61-9, Hyaluronic acid 9007-28-7, Chondroitin sulfate 10118-90-8, Minocycline 14611-51-9, Selegiline **51570-36-6, Milbemycin 51570-36-6D, Milbemycin**, derivs. 59865-13-3, Cyclosporine **73989-17-0 , Avermectin 73989-17-0D, Avermectin**, derivs. 75847-73-3, Enalapril 140207-92-7
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(carprofen and derivs. for treatment or prevention of early stages of degeneration of articular cartilage or subchondral bone, and use with other agents)
IT **51570-36-6, Milbemycin 51570-36-6D, Milbemycin**, derivs. **73989-17-0, Avermectin 73989-17-0D, Avermectin**, derivs.
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(carprofen and derivs. for treatment or prevention of early stages of degeneration of articular cartilage or subchondral bone, and use with other agents)
RN 51570-36-6 HCAPLUS
CN Milbemycin (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 51570-36-6 HCAPLUS
CN Milbemycin (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 73989-17-0 HCAPLUS

CN Avermectin (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 73989-17-0 HCAPLUS
CN Avermectin (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L32 ANSWER 2 OF 20 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2001:301220 HCAPLUS
TITLE: Impact of **doramectin** treatment at the time of feedlot entry on the productivity of yearling steers with natural nematode infections
AUTHOR(S): MacGregor, D. Scott; Yoder, Darwin R.; Rew, Robert S.
CORPORATE SOURCE: Livestock Consulting Services, Jerome, ID, 83338, USA
SOURCE: Am. J. Vet. Res. (2001), 62(4), 622-624
CODEN: AJVRAH; ISSN: 0002-9645
PUBLISHER: American Veterinary Medical Association
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Objective-To measure the redn. in fecal nematode egg counts and productivity impact of treatment of yearling steers with doramectin at entry into the feedlot, compared with control steers treated only with fenthion. Animals-6,096 crossbred yearling steers with a mean (.+-. SD) body wt. of 377.0 (.+-. 37) kg. Procedure-Steers were **implanted** with zeranol and alternately sepd. to fill each of 24 pens. Groups of steers within 12 matched pairs of pens were randomly allocated to treatment with doramectin or no treatment with doramectin for internal nematodes. Fecal samples were collected from approx. every twentieth steer from each pen at day 0 and at reimplant (approx day 60). Each steer was weighed on day 0 and at reimplant and then mean body wts. of steers per pen were detd. at 120 to 140 days after trial initiation. Results-Treatment steers had a significantly lower fecal egg count at reimplant than control steers. Treatment steers had a significantly greater mean daily gain during the study, significantly greater feed consumption, significantly lower feed-to-gain ratio, and significantly better quality carcass grades at slaughter. Conclusions and Clin. Relevance-Under the conditions of our trial, there was a significant fecal egg count redn. response to doramectin treatment, which resulted in significantly improved productivity. Results of economic anal. of return on investment indicated that even with low egg counts in heavy body wt. cattle, nematode egg count redn. with doramectin significantly improved returns.
CC 1 (Pharmacology)
REFERENCE COUNT: 5
REFERENCE(S): (1) Johnson, E; Compend Contin Educ Pract Vet 1998, PS116
(2) Jones, R; Vet Parasitol 1993, V49, P27 HCAPLUS
(3) Logan, N; Vet Parasitol 1993, V49, P67 HCAPLUS
(4) Rew, R; Int J Parasitol 1999, V29, P177 MEDLINE
(5) Stoll, N; Parasitology 1930, V22, P116

L32 ANSWER 3 OF 20 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:885987 HCAPLUS
DOCUMENT NUMBER: 135:40358

TITLE: The behaviour of **doramectin** in the gastrointestinal tract, its secretion in bile and pharmacokinetic disposition in the peripheral circulation after oral and intravenous administration to sheep

AUTHOR(S): Hennessy, D. R.; Page, S. W.; Gottschall, D.
CORPORATE SOURCE: CSIRO Animal Production, McMaster Laboratory, Blacktown, NSW 2148, Australia

SOURCE: J. Vet. Pharmacol. Ther. (2000), 23(4), 203-213
CODEN: JVPTD9; ISSN: 0140-7783
PUBLISHER: Blackwell Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Sheep were "compartmentalized" by surgically **implanting** cannulae in the rumen, abomasum and terminal ileum with a re-entrant cannula inserted between the cystic duct and the duodenum to monitor bile secretion. Doramectin, contg. a trace of [3H]-doramectin, was administered both i.v. and intraruminally (i.r.) at a dosage of 150 .mu.g/kg. The pharmacokinetic behavior of [3H]-labeled products was detd. in these pools, and also in peripheral plasma, urine and feces. Parent doramectin was also detd. in plasma, abomasal digesta fluid and bile. Following i.r. administration, [3H] compds. were almost entirely assocd. with particulate digesta. A 14.5 h half-life in the rumen prolonged the presence of [3H] in the abomasum. Doramectin appeared to be degraded in abomasal digesta because only 24% of abomasal [3H] was attributed to the parent drug. Absorption of doramectin resulted in a systemic availability of 35%, of which 1.6 and 23.6% of the dose was contained in urine and biliary secretions, resp. Following i.v. administration, almost negligible quantities of [3H] were secreted into the rumen or abomasum and only 2.7% of the dose was excreted in urine, whereas 132% was secreted in bile. This indicated that approx. one-third of biliary metabolites were enterohepatically recycled with biliary metabolites, elevating the proportion of [3H] in fluid digesta in the small intestine. Passage of the i.r.-administered drug through the gastrointestinal tract (GIT) resulted in virtually complete fecal excretion of [3H] within 5 days, whereas the continued secretion of i.v.-administered [3H] in bile prolonged the presence of [3H] in the GIT, with fecal clearance not being complete for at least 10 days. This multi-compartmental study has provided more information on the behavior of doramectin than can be obtained from examg. drug disposition in the peripheral circulation alone. With this knowledge, it is anticipated that opportunities for improving drug performance will be identified.

CC 1-2 (Pharmacology)
ST **doramectin** pharmacokinetics digestive tract bile sheep
IT Stomach, ruminant
(abomasum; **doramectin** behavior in gastrointestinal tract, secretion in bile and pharmacokinetics in peripheral circulation after oral and i.v. administration to sheep)
IT Bile
Blood plasma
Digestive tract
Feces
Sheep

Stomach, ruminant
Urine
(**doramectin** behavior in gastrointestinal tract, secretion in bile and pharmacokinetics in peripheral circulation after oral and i.v.
administration to sheep)

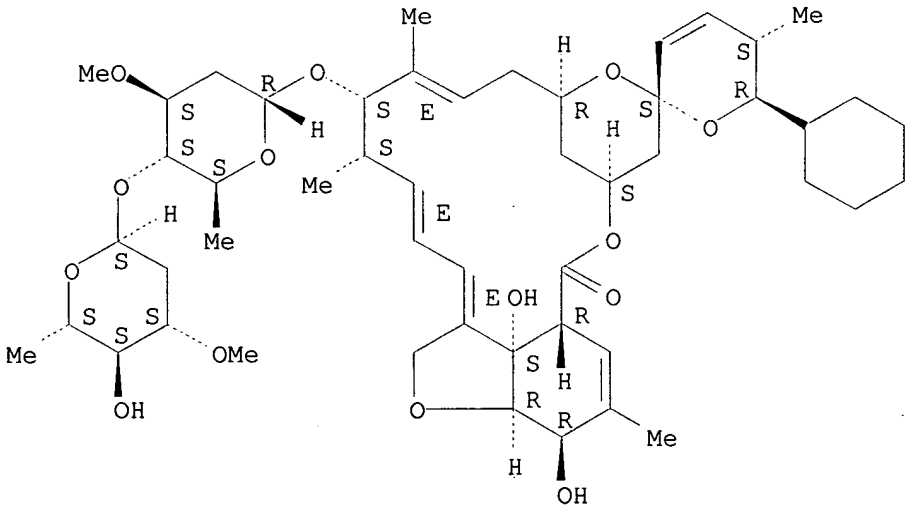
IT Intestine
(ileum; **doramectin** behavior in gastrointestinal tract, secretion in bile and pharmacokinetics in peripheral circulation after oral and i.v. administration to sheep)

IT **117704-25-3, Doramectin**
RL: BPR (Biological process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(**doramectin** behavior in gastrointestinal tract, secretion in bile and pharmacokinetics in peripheral circulation after oral and i.v.
administration to sheep)

IT **117704-25-3, Doramectin**
RL: BPR (Biological process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(**doramectin** behavior in gastrointestinal tract, secretion in bile and pharmacokinetics in peripheral circulation after oral and i.v.
administration to sheep)

RN 117704-25-3 HCAPLUS
CN Avermectin A1a, 25-cyclohexyl-5-O-demethyl-25-de(1-methylpropyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



REFERENCE COUNT: 21
REFERENCE(S):
(1) Ali, D; International Journal for Parasitology 1995, V25, P63 HCAPLUS
(2) Baggot, J; Journal of Veterinary Pharmacology and Therapeutics 1994, V17, P409 HCAPLUS
(4) Bogan, J; Journal of Veterinary Pharmacology and

Therapeutics 1988, V11, P260 HCAPLUS
(5) Dobson, A; Federation Proceedings 1967, V26, P994 HCAPLUS
(7) Hennessy, D; Journal for Veterinary Pharmacology and Therapeutics 1985, V8, P270 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L32 ANSWER 4 OF 20 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:420955 HCAPLUS
DOCUMENT NUMBER: 133:48896
TITLE: Long-acting antiparasitic **doramectin** formulations
INVENTOR(S): Harding, Valerie Denise; Wicks, Stephen Richard; Lukas, Timothy Michael; Milojevic, Snezana
PATENT ASSIGNEE(S): Pfizer Ltd., UK; Pfizer Inc.
SOURCE: PCT Int. Appl., 12 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

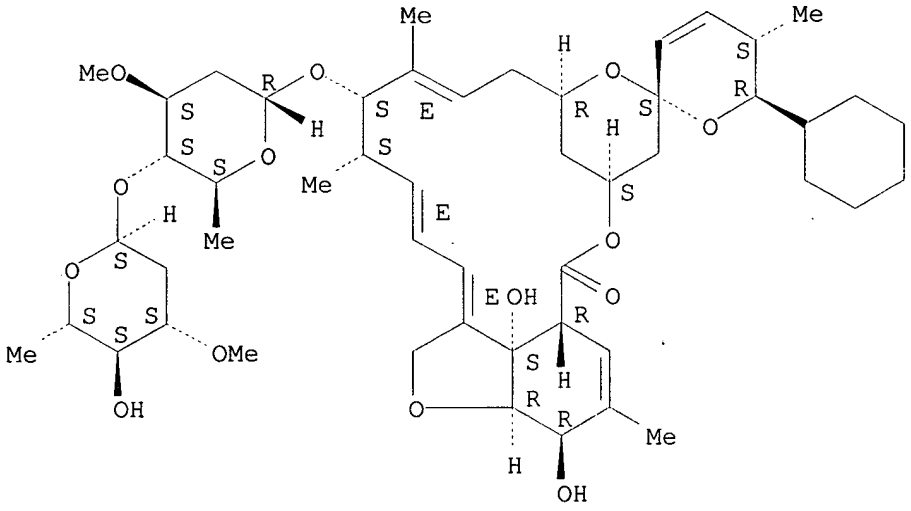
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000035445	A1	20000622	WO 1999-IB1854	19991122

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: GB 1998-27727 A 19981216
AB The title formulations suitable for injection, comprise doramectin at 1-11 % wt./vol. in a solvent comprising castor oil at 25-80 % by vol. and either Et oleate at 20-75 % by vol. or fractionated coconut oil at 20-75 % by vol. with optional auxiliaries.
IC ICM A61K031-365
ICS A61K047-44
CC 63-6 (Pharmaceuticals)
ST veterinary antiparasitic **doramectin** injection castor oil
IT Parasiticides
(ecto-; long-acting antiparasitic **doramectin** injection formulations)
IT Parasiticides
(endoparasiticides; long-acting antiparasitic **doramectin** injection formulations)
IT Coconut oil
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(fractionated; long-acting antiparasitic **doramectin** injection formulations)
IT Drug delivery systems
(injections, **sustained release**; long-acting

antiparasitic **doramectin** injection formulations)
IT Cattle
(long-acting antiparasitic **doramectin** injection formulations)
IT Castor oil
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(long-acting antiparasitic **doramectin** injection formulations)
IT 111-62-6, Ethyl oleate 77466-09-2, Miglyol 840 **117704-25-3, Doramectin**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(long-acting antiparasitic **doramectin** injection formulations)
IT **117704-25-3, Doramectin**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(long-acting antiparasitic **doramectin** injection formulations)
RN 117704-25-3 HCAPLUS
CN Avermectin A1a, 25-cyclohexyl-5-O-demethyl-25-de(1-methylpropyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L32 ANSWER 5 OF 20 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:268740 HCAPLUS
DOCUMENT NUMBER: 133:125014
TITLE: Ophthalmic and topical dosage form new animal drugs; **milbemycin** oxime solution
CORPORATE SOURCE: Food and Drug Administration, USA
SOURCE: Fed. Regist. (2000), 65(51), 13904-13905, 15 Mar 2000
CODEN: FEREAC; ISSN: 0097-6326
PUBLISHER: Superintendent of Documents
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The Food and Drug Administration (FDA) is amending, under the Federal Food, Drug, and Cosmetic Act, the animal drug regulations to reflect approval of a new animal drug application (NADA) filed by Novartis Animal Health US, Inc. The NADA provides for veterinary prescription use of milbemycin oxime soln. to treat ear mite infestations in cats and kittens

8 wk of age and older.
CC 63-2 (Pharmaceuticals)
ST **milbemycin** soln **ear** mite cat std
IT Drug delivery systems
(solns., **ear**; stds. for **milbemycin** oxime soln. for treatment of **ear** mite infestations in cats)
IT Cat (Felis catus)
Mite and Tick
Standards, legal and permissive
(stds. for **milbemycin** oxime soln. for treatment of **ear** mite infestations in cats)
IT 129496-10-2, **Milbemycin** oxime
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(stds. for **milbemycin** oxime soln. for treatment of **ear** mite infestations in cats)

L32 ANSWER 6 OF 20 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:227347 HCAPLUS
DOCUMENT NUMBER: 132:256015
TITLE: Pharmaceutical **implants** containing parasiticides
INVENTOR(S): Kenison, Dale C.; Spurlin, Stanford R.
PATENT ASSIGNEE(S): Ivy Animal Health, Inc., USA
SOURCE: Eur. Pat. Appl., 8 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 990450	A2	20000405	EP 1999-307736	19990930
EP 990450	A3	20000802		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
AU 9948737	A1	20000406	AU 1999-48737	19990915
BR 9904379	A	20000905	BR 1999-4379	19990929

PRIORITY APPLN. INFO.: US 1998-163646 A 19980930
AB A pharmaceutical pellet system, which delivers both immediate and long term control of parasite infestation in an animal as part of a single **implant** procedure, includes an **implanter** app. for s.c. **implanting** parasiticidal pellets in an animal through the bore of a hypodermic needle which is operably coupled to a pellet magazine, and a plurality of pellets sized to be **implanted** through the needle and positioned in the magazine for selective alignment of a pellet with a needle. The pellets include at least one immediate release parasiticidal agent first dose pellet and at least one extended release parasiticidal agent dose second pellet. The combined pellets are packaged in the magazine in sequential order for simultaneous delivery of an immediate dose and an extended dose as part of a single injection. Sustained-release pellets were prepd. contg. ivermectin in a PEG matrix.
IC ICM A61M037-00
ICS A61K009-00; A61K009-20
CC 63-6 (Pharmaceuticals)
ST parasiticide **sustained release** pellet **implant**
IT Drug delivery systems

(**implants, sustained-release;**
pharmaceutical **implants** contg. parasiticides)
IT Parasiticides
(pharmaceutical **implants** contg. parasiticides)
IT 70288-86-7, Ivermectin
RL: PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(pharmaceutical **implants** contg. parasiticides)
IT 43210-67-9, Fenbendazole **51570-36-6, Milbemycin 73989-17-0, Avermectin** 103055-07-8, Lufenuron
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical **implants** contg. parasiticides)
IT **51570-36-6, Milbemycin 73989-17-0, Avermectin**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical **implants** contg. parasiticides)
RN 51570-36-6 HCAPLUS
CN Milbemycin (9CI) (CA INDEX NAME)

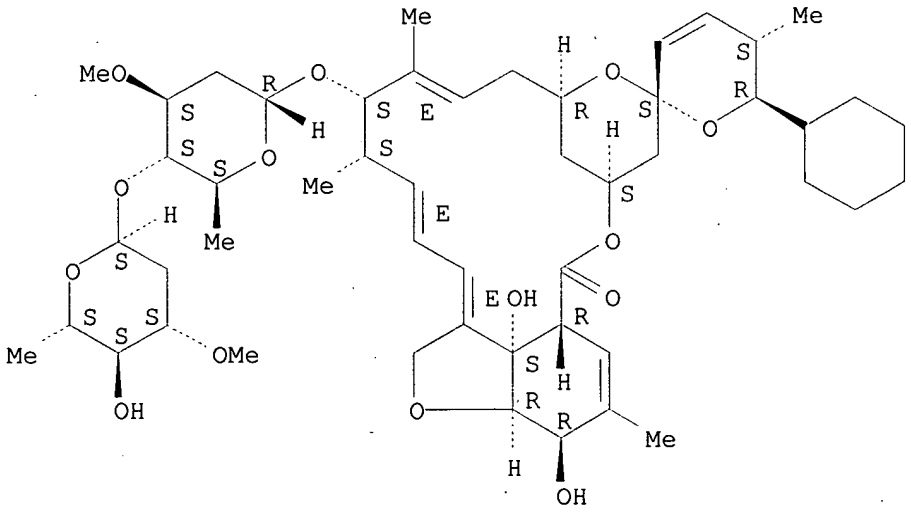
*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 73989-17-0 HCAPLUS
CN Avermectin (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L32 ANSWER 7 OF 20 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:733398 HCAPLUS
DOCUMENT NUMBER: 132:303001
TITLE: Persistent activity of **doramectin** and ivermectin in the prevention of cutaneous myiasis in cattle experimentally infested with Cochliomyia hominivorax
AUTHOR(S): Anziani, O. S.; Flores, S. G.; Moltedo, H.; Derozier, C.; Guglielmone, A. A.; Zimmermann, G. A.; Wanker, O.
CORPORATE SOURCE: EEA INTA Rafaela, Santa Fe, Argent.
SOURCE: Vet. Parasitol. (2000), 87(2,3), 243-247
CODEN: VPARDI; ISSN: 0304-4017
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A study was conducted to evaluate the activity of a single administration of doramectin or ivermectin against severe, induced infestations of Cochliomyia hominivorax. Twenty-four Holstein bull calves were allocated to four groups of six animals each and treated either with saline, doramectin 1%, or either one of two formulations of ivermectin 1% at a dose rate of 200 .mu.g/kg. On Day 12 after treatment, each calf was anesthetized and two wounds were created on the left side of the shoulder and rump of each calf and 2 h later, each wound was **implanted** with 100 newly hatched larvae of C. hominivorax. On Day 15 after treatment, the procedure was repeated on the right side of each calf. Wounds were examd. daily for 5 days and evidence of live larvae was recorded. Doramectin provided redn. in myiasis of 90.9 and 83.3% at 12 and 15 days after treatment, resp., compared to the saline control treatment ($P < 0.0001$). In contrast, there were no significant differences in the no. of calves with myiasis between those treated with either of the ivermectin formulations and the saline control.
CC 1-5 (Pharmacology)

Section cross-reference(s): 5
ST cattle Cochliomyia myiasis **doramectin** ivermectin
IT Cochliomyia hominivorax
Fly (Diptera)
(activity of **doramectin** and ivermectin in prevention of cutaneous myiasis in cattle infested with Cochliomyia hominivorax)
IT 70288-86-7, Ivermectin **117704-25-3, Doramectin**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(activity of **doramectin** and ivermectin in prevention of cutaneous myiasis in cattle infested with Cochliomyia hominivorax)
IT **117704-25-3, Doramectin**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(activity of **doramectin** and ivermectin in prevention of cutaneous myiasis in cattle infested with Cochliomyia hominivorax)
RN 117704-25-3 HCAPLUS
CN Avermectin A1a, 25-cyclohexyl-5-O-demethyl-25-de(1-methylpropyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



REFERENCE COUNT: 15
REFERENCE(S):
(1) Anziani, O; Ann NY Acad Sci 1996, V791, P443 HCAPLUS
(3) Benitez Usher, C; Vet Parasitol 1997, V72, P215 HCAPLUS
(10) Moya Borja, G; Vet Parasitol 1993, V49, P95 HCAPLUS
(11) Moya Borja, G; Vet Parasitol 1997, V72, P101 HCAPLUS
(12) Muniz, R; Vet Parasitol 1995, V58, P155 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L32 ANSWER 8 OF 20 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:613599 HCAPLUS

DOCUMENT NUMBER: 131:233575
TITLE: Liquid polymeric compositions for **controlled release** of bioactive substances
INVENTOR(S): Chern, Rey T.; Zingerman, Joel R.
PATENT ASSIGNEE(S): Merck & Co., Inc., USA
SOURCE: PCT Int. Appl., 42 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9947073	A1	19990923	WO 1999-US5938	19990318
W: AE, AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TJ, TM, TR, TT, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9930100	A1	19991011	AU 1999-30100	19990318
BR 9908893	A	20001128	BR 1999-8893	19990318
EP 1063942	A1	20010103	EP 1999-911462	19990318
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, SI, LT, LV, FI, RO				
NO 2000004616	A	20000915	NO 2000-4616	20000915

PRIORITY APPLN. INFO.:		
US 1998-79574	P	19980319
GB 1998-15801	A	19980721
WO 1999-US5938	W	19990318

AB Controlled release of hydrophobic bioactive substances in vivo over an extended time period and without "bursts" of drug release is achieved using a liq. polymeric compn. including a polymer such as poly(lactide-co-glycolide) copolymer in a mixt. of hydrophilic and lipophilic solvents. Long-acting injectable formulations were prepd. contg. glycolide-lactide copolymer, ivermectin or eprinomectin, triacetin, and glycerol formal.

IC ICM A61F002-02
ICS A61K009-50; B01J013-02; B32B005-16
CC 63-6 (Pharmaceuticals)
ST **controlled release** injection polyester
IT Drug delivery systems
(**controlled-release**, injections; liq. polymeric compns. for **controlled release** of drugs)
IT Polyesters, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(dilactone-based; liq. polymeric compns. for **controlled release** of drugs)
IT Solvents
(hydrophilic and lipophilic; liq. polymeric compns. for **controlled release** of drugs)
IT Drug delivery systems
(injections, **sustained release**; liq. polymeric compns. for **controlled release** of drugs)

IT Drug bioavailability
(liq. polymeric compns. for **controlled release** of drugs)
IT 102-76-1, Triacetin 4740-78-7, 1,3-Dioxan-5-ol 5464-28-8, Glycerol formal
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(liq. polymeric compns. for **controlled release** of drugs)
IT 120068-37-3, Fipronil
RL: PEP (Physical, engineering or chemical process); PRP (Properties); THU
(Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(liq. polymeric compns. for **controlled release** of drugs)
IT 26780-50-7, Glycolide-lactide copolymer 70288-86-7, Ivermectin
73989-17-0, Avermectin 123997-26-2, Eprinomectin
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES
(Uses)
(liq. polymeric compns. for **controlled release** of drugs)
IT 50-50-0, Estradiol benzoate 57-83-0, Progesterone, biological studies
68-22-4, Norethisterone 10161-34-9, Trenbolone acetate
51570-36-6, Milbemycin 149757-07-3 163120-03-4, Nodulisporic acid a
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(liq. polymeric compns. for **controlled release** of drugs)
IT **73989-17-0, Avermectin**
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES
(Uses)
(liq. polymeric compns. for **controlled release** of drugs)
RN 73989-17-0 HCAPLUS
CN Avermectin (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
IT **51570-36-6, Milbemycin**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(liq. polymeric compns. for **controlled release** of drugs)
RN 51570-36-6 HCAPLUS
CN Milbemycin (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
REFERENCE COUNT: 1
REFERENCE(S): (1) Carrio; Journal of Controlled Release 1995, V37(1-2), P113 HCAPLUS

L32 ANSWER 9 OF 20 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:257952 HCAPLUS
DOCUMENT NUMBER: 131:49254
TITLE: **Implantation** or injectable dosage form new animal drugs; **doramectin**
CORPORATE SOURCE: Food and Drug Administration, USA

SOURCE: Fed. Regist. (1999), 64(53), 13508-13509, 19 Mar 1999
CODEN: FEREAC; ISSN: 0097-6326
PUBLISHER: Superintendent of Documents
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The Food and Drug Administration (FDA) is amending, under the Federal Food, Drug, and Cosmetic Act, the animal drug regulations to reflect approval of a supplemental new animal drug application (NADA) filed by Pfizer, Inc. The supplemental NADA provides for extended use of doramectin in cattle for persistent control of nematodes including Haemonchus placei for 14 days after treatment.

CC 63-2 (Pharmaceuticals)
Section cross-reference(s): 1

ST **doramectin** anthelmintic cattle nematode std

IT Anthelmintics
Cattle
Haemonchus placei
Nematode (Nematoda)
Standards, legal and permissive
(stds. for **doramectin** as anthelmintic for cattle)

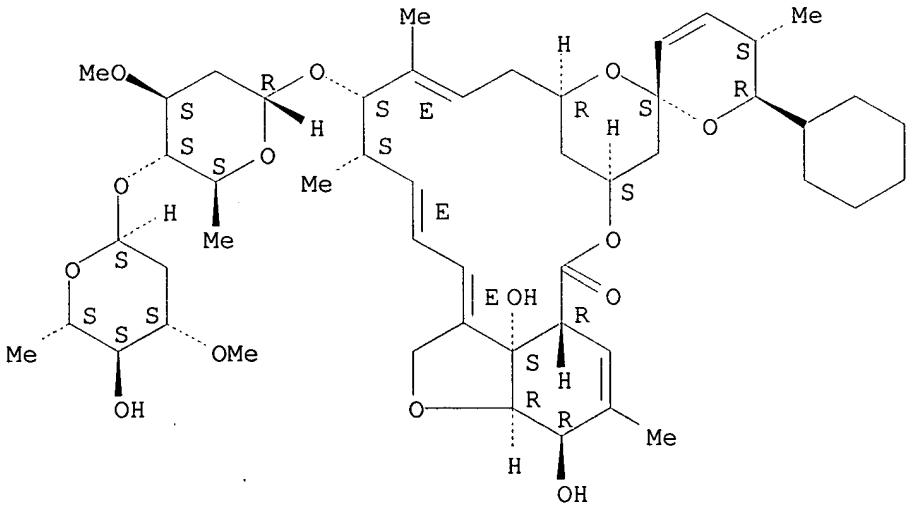
IT **117704-25-3, Doramectin**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(stds. for **doramectin** as anthelmintic for cattle)

IT **117704-25-3, Doramectin**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(stds. for **doramectin** as anthelmintic for cattle)

RN 117704-25-3 HCAPLUS

CN Avermectin A1a, 25-cyclohexyl-5-O-demethyl-25-de(1-methylpropyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L32 ANSWER 10 OF 20 HCAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1998:231109 HCAPLUS
DOCUMENT NUMBER: 129:76028
TITLE: Effects of preventive anthelmintic treatment on acquired resistance to gastrointestinal nematodes in naturally infected cattle
AUTHOR(S): Claerebout, E.; Dorny, P.; Vercruysse, J.; Agneessens, J.; Demeulenaere, D.
CORPORATE SOURCE: Faculty of Veterinary Medicine, Department of Parasitology, University of Gent, Merelbeke, 9820, Belg.
SOURCE: Vet. Parasitol. (1998), 76(4), 287-303
CODEN: VPARDI; ISSN: 0304-4017
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The objective of this study was to investigate the influence of different types of chemoprophylaxis in first season grazing calves on their resistance against a natural reinfection with Ostertagia ostertagi and Cooperia oncophora in the second grazing season. Thirty helminth-naive crossbred calves were randomly divided in three groups of 10 animals. The animals of group B received an ivermectin sustained release bolus on day 0. The calves of group D were treated on days 0 and 56 with a s.c. injection of doramectin (0.2 mg kg-1 BW). Group C was the untreated control group ('immune' controls). Although exposure to gastrointestinal nematodes in the first grazing season was only limited, the chemoprophylactic treatments in groups B and D resulted in three distinctly different infection levels (group C>group D>group B). At the start of the second grazing season, six helminth-naive steers (group N, 'susceptible' controls) were turned out together with the second season animals. After 3 wk of grazing, the 'susceptible' controls were slaughtered, together with four animals from each other group. Parasitol. and immunol. parameters indicated that resistance to reinfection with Ostertagia was reduced in the chemoprophylactic treated animals, and was neg. related to the degree of suppression of host-parasite contact in the first grazing season (group C>group D>group B>group N). None of the groups had developed a complete resistance against Cooperia yet. A neg. relationship was obsd. between redn. of first grazing season exposure, and wt. gains early in the second grazing season. The remaining animals stayed on pasture until the beginning of Nov. At the end of the second grazing season, levels of acquired resistance against Ostertagia infection were similar in all groups, and all animals had become immune against Cooperia. No effect of first year chemoprophylaxis on total wt. gains could be demonstrated. Because of discrepancy between pasture larval counts and tracer worm counts, it was not possible to draw firm conclusions on the effect of chemoprophylaxis on pasture infestation levels in the second year.

CC 1-5 (Pharmacology)
Section cross-reference(s): 63

IT Anthelmintics
Cattle
Cooperia oncophora
Gastrointestinal tract

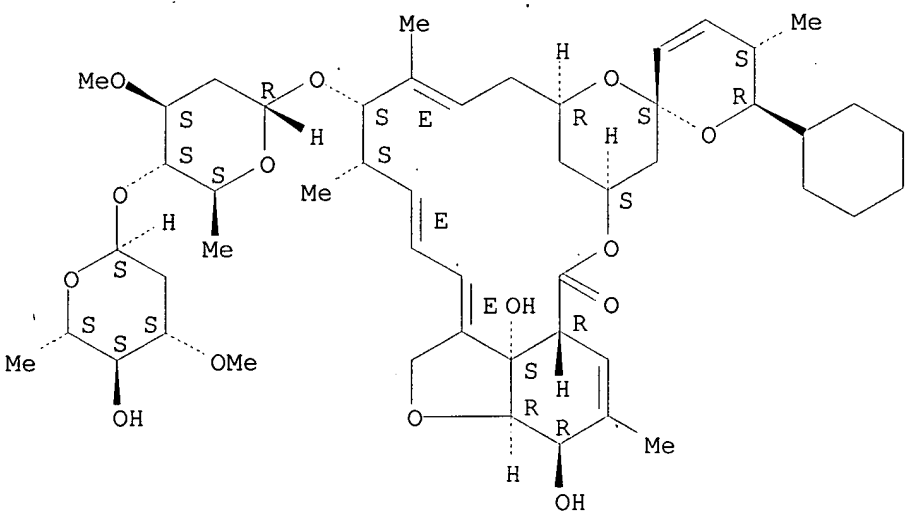
Immunity
Nematode (Nematoda)
Ostertagia ostertagi
Sustained release drug delivery systems
(preventive anthelmintic treatment effect on acquired resistance to gastrointestinal nematodes in naturally infected cattle)

IT 70288-86-7, Ivermectin **117704-25-3, Doramectin**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preventive anthelmintic treatment effect on acquired resistance to gastrointestinal nematodes in naturally infected cattle)

IT **117704-25-3, Doramectin**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preventive anthelmintic treatment effect on acquired resistance to gastrointestinal nematodes in naturally infected cattle)

RN 117704-25-3 HCAPLUS
CN Avermectin A1a, 25-cyclohexyl-5-O-demethyl-25-de(1-methylpropyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L32 ANSWER 11 OF 20 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:146652 HCAPLUS
DOCUMENT NUMBER: 128:189505
TITLE: Insecticidal device
INVENTOR(S): Shasha, Baruch S.; McGuire, Michael R.; Hu, Xing Ping;
Prokopy, Ronald J.
PATENT ASSIGNEE(S): United States Dept. of Agriculture, USA
SOURCE: U.S., 7 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5720968	A	19980224	US 1996-701088	19960821
WO 9807315	A1	19980226	WO 1997-US14493	19970818
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9740720	A1	19980306	AU 1997-40720	19970818
EP 921724	A1	19990616	EP 1997-938380	19970818
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				

PRIORITY APPLN. INFO.: US 1996-701088 A 19960821
WO 1997-US14493 W 19970818

AB The invention is a device for delivering an insecticide, made of (a) an outer layer comprising a porous water-insol. polymer; (b) an inner layer in contact with the outer layer, the inner layer comprising a water-sol. feeding stimulant and a carbohydrate which is at least partially gelatinized; and (c) a toxicant which is present on or in the outer layer, the inner layer, or both. The pests for which the device may be used are those that can be attracted to an object to feed and/or lay eggs, such as the apple maggot fly, the Mediterranean fruit fly, the house fly, the oriental fruit fly, the blueberry fruit fly, the olive fruit fly, the melon fruit fly, and the Mexican fruit fly as well as other flies, beetles, wasps, moths, cockroaches, and any other insect that can be lured to a device for feeding or egg laying. The porous water-insol. polymeric materials are pits, shellacs, linseed oil and other water-sol. or water-suspendible material that becomes insol. upon drying. Examples of water-sol. feeding stimulants are sucrose, glucose, fructose, molasses, maltodextrin, and corn syrup as well as corn flour, gluten or other sugary or proteinaceous and lipid materials. Examples of carbohydrates are corn flour, corn starch, wheat starch, and potato starch. Toxicants which may be used are dimethoate, phloxine B, avermectin, azinphosmethyl, diazinon, permethrin, imidacloprid, malathion, methomyl, etc. A high boiling liq. such as glycerin may optionally be added to the carbohydrate first layer to prevent cracking.

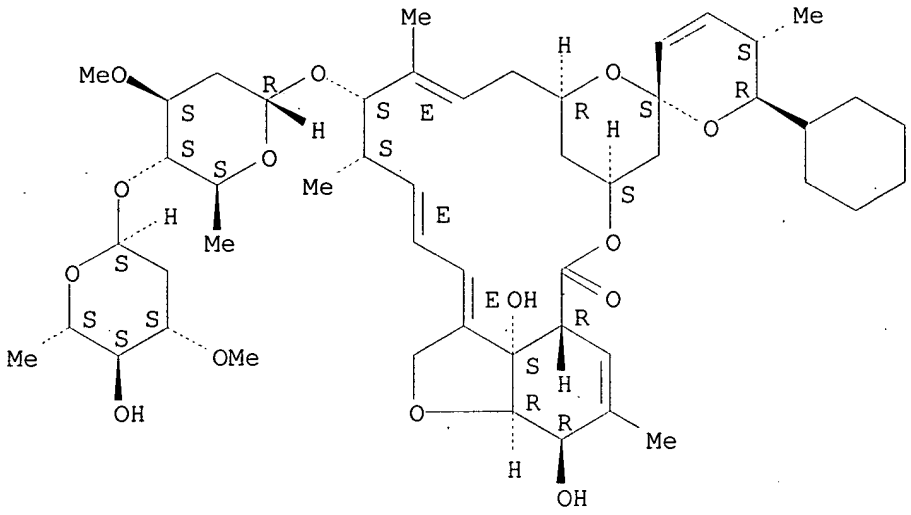
IC ICM A01N025-10
NCL 424410000
CC 5-4 (Agrochemical Bioregulators)
ST **sustained release** insecticide device
IT Insecticides
(**controlled-release**; insecticidal device)
IT 60-51-5, Dimethoate 86-50-0, Azinphosmethyl 121-75-5, Malathion 333-41-5, Diazinon 16752-77-5, Methomyl 18472-87-2, Phloxine B 52645-53-1, Permethrin **73989-17-0**, **Avermectin** 138261-41-3, Imidacloprid
RL: AGR (Agricultural use); BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)

(insecticidal device contg.)
IT **73989-17-0, Avermectin**
RL: AGR (Agricultural use); BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(insecticidal device contg.)
RN 73989-17-0 HCAPLUS
CN Avermectin (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L32 ANSWER 12 OF 20 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1997:557130 HCAPLUS
DOCUMENT NUMBER: 127:195289
TITLE: **Implantation** or injectable dosage form new animal drugs; **doramectin**
CORPORATE SOURCE: Food & Drug Administration, Food & Drug Administration, Rockville, MD, 20855, USA
SOURCE: Fed. Regist. (1997), 62(162), 44409-44410, 21 Aug 1997
CODEN: FEREAC; ISSN: 0097-6326
PUBLISHER: Superintendent of Documents
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The Food and Drug Administration (FDA) is amending the animal drug regulations to reflect approval of a supplemental new animal drug application (NADA), under the Federal Food, Drug, and Cosmetic Act, for a 1% doramectin injectable soln. as anthelmintic in cattle to control infections and to protect from reinfection with Cooperia punctata and Dictyocaulus viviparus for 28 days after treatment. This supplemental NADA also amends the wording of the claim for protection against infection
or reinfection with Ostertagia ostertagi for 21 days and incorporates the claim into the new indication statement.
CC 63-2 (Pharmaceuticals)
Section cross-reference(s): 1
ST **doramectin** injection anthelmintic cattle std
IT Cooperia punctata
Dictyocaulus viviparus
Ostertagia ostertagi
(infections with; stds. for **doramectin** injections as anthelmintic in cattle)
IT Anthelmintics
Cattle
Injections (drug delivery systems)
Legal standards
(stds. for **doramectin** injections as anthelmintic in cattle)
IT **117704-25-3, Doramectin**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(stds. for **doramectin** injections as anthelmintic in cattle)
IT **117704-25-3, Doramectin**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(stds. for **doramectin** injections as anthelmintic in cattle)
RN 117704-25-3 HCAPLUS
CN Avermectin A1a, 25-cyclohexyl-5-O-demethyl-25-de(1-methylpropyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L32 ANSWER 13 OF 20 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1995:364211 HCAPLUS
DOCUMENT NUMBER: 122:114945
TITLE: **controlled-release** antiparasitic compositions
INVENTOR(S): Hennessy, Desmond Ronald; Ashes, John Richard; Scott, Trevor William; Gulati, Suresh Kumar; Steel, John Winston
PATENT ASSIGNEE(S): Commonwealth Scientific and Industrial Research Organization, Australia; Meat Research Corp.
SOURCE: PCT Int. Appl., 29 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9427598	A1	19941208	WO 1994-AU272	19940524
W: AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, GE, HU, JP, KG, KP, KR, KZ, LK, LU, LV, MD, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, US, UZ, VN				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA 2163455	AA	19941208	CA 1994-2163455	19940524
AU 9467902	A1	19941220	AU 1994-67902	19940524
AU 687062	B2	19980219		
BR 9406627	A	19960206	BR 1994-6627	19940524
EP 705101	A1	19960410	EP 1994-916095	19940524
R: DE, ES, FR, GB, IT				
ZA 9403647	A	19950127	ZA 1994-3647	19940525

US 5840324 A 19981124 US 1996-549755 19960313
PRIORITY APPLN. INFO.: AU 1993-9030 19930526
WO 1994-AU272 19940524

AB The delivery of anti-parasitic agents to ruminant animals in a controlled manner to enable the agent to have max. effect on the parasite for longer times than is possible with conventional formulations is described. The compns. comprise a benzimidazole, macrocyclic lactone, organophosphate, salicylanilide/substituted phenol, tetramisole or pyrimidine anti-parasitic agent, dispersed in a medium the soly. characteristics of which are such as to ensure that, following oral administration, controlled amts. of the anti-parasitic agent become available to the parasite, either directly or by absorption into the ruminant blood plasma, during passage of the compn. through the rumen, the abomasum and the intestine. A 3-stage release antiparasitic formulation was prepd. from benzimidazole, vegetable oil, emulsification with caseins, freeze-drying and treatment with formalin.

IC ICM A61K031-415
ICS A61K031-365; A61K031-665; A61K031-615; A61K031-425; A61K031-505; A61K009-14; A61K009-52

CC 63-6 (Pharmaceuticals)

ST parasiticide **controlled release**

IT Cattle
Intestine
Stomach, ruminant
(**controlled-release** antiparasitic compns.)

IT Aldehydes, biological studies
Caseins, biological studies
Crosslinking agents
Tannins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**controlled-release** antiparasitic compns.)

IT Parasiticides
(**controlled-release**; **controlled-release** antiparasitic compns.)

IT Lactones
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(macrolides, **controlled-release** antiparasitic compns.)

IT 87-17-2, Salicylanilide 148-79-8, Thiabendazole 5036-02-2, Tetramisole
7664-38-2D, Phosphoric acid, esters with org. alcs. 14255-87-9, Parbendazole 20559-55-1, Oxibendazole 26097-80-3, Cambendazole 31430-15-6, Flubendazole 31431-39-7, Mebendazole 31431-43-3, Ciclobendazole 43210-67-9, Fenbendazole **51570-36-6**, **Milbemycin** 53716-50-0, Oxfendazole 54029-12-8, Albendazole sulfoxide 54965-21-8, Albendazole 68786-66-3, Triclabendazole 70288-86-7, Ivermectin 71751-41-2, Abamectin **73989-17-0**, **Avermectin** 90509-02-7, Luxabendazole 113507-06-5, Moxidectin **117704-25-3**, **Doramectin**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**controlled-release** antiparasitic compns.)

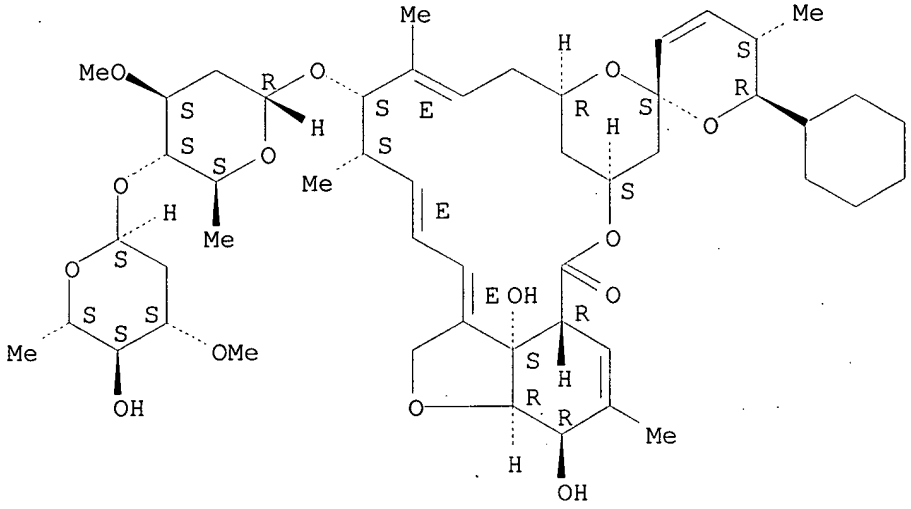
IT 50-00-0, Formaldehyde, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**controlled-release** antiparasitic compns.)

IT **51570-36-6, Milbemycin 73989-17-0, Avermectin 117704-25-3, Doramectin**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**controlled-release** antiparasitic compns.)
RN 51570-36-6 HCAPLUS
CN Milbemycin (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 73989-17-0 HCAPLUS
CN Avermectin (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 117704-25-3 HCAPLUS
CN Avermectin A1a, 25-cyclohexyl-5-O-demethyl-25-de(1-methylpropyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L32 ANSWER 14 OF 20 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1993:574170 HCAPLUS
DOCUMENT NUMBER: 119:174170
TITLE: Juvenile hormone agents for systemically treating ectoparasites
INVENTOR(S): Miller, Thomas A.
PATENT ASSIGNEE(S): Virbac S.A., Fr.
SOURCE: Eur. Pat. Appl., 32 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

EP 549441	A1	19930630	EP 1992-403478	19921221
EP 549441	B1	19970806		
R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, NL				
AU 9230145	A1	19930624	AU 1992-30145	19921215
AU 660205	B2	19950615		
AT 156357	E	19970815	AT 1992-403478	19921221
ES 2108099	T3	19971216	ES 1992-403478	19921221
ZA 9209950	A	19931103	ZA 1992-9950	19921222
JP 06211792	A2	19940802	JP 1992-342774	19921222
US 5439924	A	19950808	US 1994-210135	19940317
US 5728719	A	19980317	US 1995-403414	19950314
PRIORITY APPLN. INFO.:			US 1991-812430	19911223
			US 1992-980591	19921123
			US 1994-210135	19940317

AB Ectoparasites are battled systemically in warm-blooded animals by administering heterocyclic compds. I (R1 = substituted pyridinyl, substituted pyridazinyl, etc.; R2, R3 = H, halo, Me; R4 = halo, Me; R5, R6 = H, halo, C1-4 haloalkyl, C1-4 haloalkoxy; X, Y, Z = O, S, CH2; m = 0-4; n = 0-2) as an ectoparasite ovicide. Pharmaceutical compns. contain I and a parasiticide (avermectin, milbemycin, ivermectin, milbemycin oxime, and moxidectin, or their derivs. and mixts.). Formulations contg. pyriproxifen (II) alone or in combination with moxidectin or milbemycin oxime are presented. II given orally to cats and rabbits was effective against fleas and ticks, resp.

IC ICM A61K031-44
ICS A61K031-495; A61K031-50; A61K031-51; A61K031-53; A61K031-425; A61K031-54; A23K001-16

CC 1-5 (Pharmacology)
Section cross-reference(s): 5, 63

IT Parasiticides
(endo-, pyriproxifen in combination with **avermectin** or other parasiticide for systemic ectoparasiticide and)

IT Pharmaceutical dosage forms
(**implants**, of ovicidal heterocyclic compds. and parasiticides, for systemic control of ectoparasites)

IT **51570-36-6, Milbemycin 51570-36-6D, Milbemycin**, derivs. 70288-86-7, Ivermectin 70288-86-7D, Ivermectin, derivs. **73989-17-0, Avermectin 73989-17-0D, Avermectin**, derivs. 113507-06-5, Moxidectin 113507-06-5D, Moxidectin, derivs. 129496-10-2, **Milbemycin** oxime 129496-10-2D, **Milbemycin** oxime, derivs.
RL: BIOL (Biological study)
(systemic ectoparasiticides contg. heterocyclic compd. and)

IT **51570-36-6, Milbemycin 51570-36-6D, Milbemycin**, derivs. **73989-17-0, Avermectin 73989-17-0D, Avermectin**, derivs.
RL: BIOL (Biological study)
(systemic ectoparasiticides contg. heterocyclic compd. and)

RN 51570-36-6 HCAPLUS
CN Milbemycin (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 51570-36-6 HCAPLUS
CN Milbemycin (9CI) (CA INDEX NAME)

(inhibition of, **avermectin**-contg. collars for, in pets)
IT Pharmaceutical dosage forms
(**controlled-release**, of **avermectin** or **milbemycin**, collar polymeric matrix in, for flea and tick inhibition for pets)
IT Animal
(pet, **avermectin**- or **milbemycin**-contg. flea and tick collars for)
IT **51570-36-6, Milbemycin** 70288-86-7, Ivermectin **73989-17-0, Avermectin** 149029-86-7
RL: BIOL (Biological study)
(flea and tick collar for pets contg., polymeric matrix for)
IT **51570-36-6, Milbemycin 73989-17-0, Avermectin**
RL: BIOL (Biological study)
(flea and tick collar for pets contg., polymeric matrix for)
RN 51570-36-6 HCAPLUS
CN Milbemycin (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 73989-17-0 HCAPLUS
CN Avermectin (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L32 ANSWER 16 OF 20 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1993:219853 HCAPLUS
DOCUMENT NUMBER: 118:219853
TITLE: Stable parenteral compositions containing antibiotic LL-F 28249 compounds
INVENTOR(S): Cady, Susan Mancini; Steber, William David; Hayes, Phillip Wayne; Doscher, Mary Ehlers; Schwinghammer, Kurt Allen
PATENT ASSIGNEE(S): American Cyanamid Co., USA
SOURCE: Eur. Pat. Appl., 12 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 525307	A1	19930203	EP 1992-107277	19920429
EP 525307	B1	19960306		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, PT, SE				
AT 134873	E	19960315	AT 1992-107277	19920429
ES 2086022	T3	19960616	ES 1992-107277	19920429
CN 1068735	A	19930210	CN 1992-105395	19920630
CN 1046852	B	19991201		
BR 9202771	A	19930323	BR 1992-2771	19920720
JP 05194211	A2	19930803	JP 1992-213259	19920720
CA 2074348	AA	19930124	CA 1992-2074348	19920721
IL 102567	A1	19961031	IL 1992-102567	19920721
AU 9220472	A1	19930128	AU 1992-20472	19920722
AU 651229	B2	19940714		
ZA 9205522	A	19930428	ZA 1992-5522	19920722

HU 62454 A2 19930528 HU 1992-2404 19920722
PRIORITY APPLN. INFO.: US 1991-734430 19910723
AB An antibiotic selected from a group consisting of LL-F 28249.alpha., LL-F 28249.beta., LL-F 28249.gamma., etc., milbemycin, and avermectin is formulated into a microsphere, dispersed in a liq. vehicle and parenterally administered to animals for treatment of infections and infestations by helminth, nematodes, acarids, and endo- and ectoparasitic arthropods. For example, microspheres contained 23-(O-methyloxime)-F 28249.alpha. 12, glyceryl tristearate 78.2, glyceridic oil 8.7, and butylated hydroxytoluene 1.1%.
IC ICM A61K009-16
ICS A61K031-35; A61K031-71
CC 63-6 (Pharmaceuticals)
IT Pharmaceutical dosage forms
(parenterals, **sustained-release**, microspheres, antibiotic LL-F 28249 compds. as veterinary parasiticides in)
IT **51570-36-6, Milbemycin 73989-17-0, Avermectin** 102042-08-0, LL-F 28249.beta. 102042-12-6, LL-F 28249.lambda. 102042-13-7, LL-F 28249.kappa. 102042-14-8, LL-F 28249.theta. 102042-15-9, LL-F 28249.eta. 102042-16-0, LL-F 28249.zeta. 102042-17-1, LL-F 28249.delta. 102042-18-2, LL-F 28249.gamma. 102063-00-3, LL-F 28249.iota. 102063-01-4, LL-F 28249.epsilon. 102130-84-7, LL-F 28249.alpha. 133164-00-8
RL: BIOL (Biological study)
(injection contg., as veterinary parasiticide)
IT **51570-36-6, Milbemycin 73989-17-0, Avermectin**
RL: BIOL (Biological study)
(injection contg., as veterinary parasiticide)
RN 51570-36-6 HCAPLUS
CN Milbemycin (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 73989-17-0 HCAPLUS
CN Avermectin (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L32 ANSWER 17 OF 20 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1993:45753 HCAPLUS
DOCUMENT NUMBER: 118:45753
TITLE: **Sustained-release** capsule and formulations for insertion into the rumen
INVENTOR(S): Lowe, Lionel Barry; McArthur, Colin John
PATENT ASSIGNEE(S): Lilly, Eli, and Co., USA
SOURCE: Eur. Pat. Appl., 22 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 507629	A1	19921007	EP 1992-302997	19920403
EP 507629	B1	19970122		

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, MC, NL, PT, SE

AU 9213969	A1	19921008	AU 1992-13969	19920401
AU 650113	B2	19940609		
CA 2065084	AA	19921006	CA 1992-2065084	19920403
NO 9201304	A	19921006	NO 1992-1304	19920403
CN 1067810	A	19930113	CN 1992-103383	19920403
CN 1056278	B	20000913		
EP 715847	A2	19960612	EP 1996-200392	19920403
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, MC, NL, PT, SE				
AT 147972	E	19970215	AT 1992-302997	19920403
ES 2096717	T3	19970316	ES 1992-302997	19920403
HU 74907	A2	19970328	HU 1992-1135	19920403
HU 217965	B	20000528		
CZ 282457	B6	19970716	CZ 1992-1023	19920403
IL 101491	A1	19980208	IL 1992-101491	19920403
RU 2114577	C1	19980710	RU 1992-5011437	19920403
IL 118192	A1	19980816	IL 1992-118192	19920403
IL 118193	A1	19980816	IL 1992-118193	19920403
IL 118194	A1	19980924	IL 1992-118194	19920403
IL 118195	A1	19980924	IL 1992-118195	19920403
HU 219460	B	20010428	HU 1999-4520	19920403
BR 9201217	A	19921201	BR 1992-1217	19920406
JP 05097659	A2	19930420	JP 1992-84207	19920406
US 5277912	A	19940111	US 1992-863898	19920406
ZA 9202520	A	19921230	ZA 1992-2520	19920407
US 5562915	A	19961008	US 1993-163842	19931207
AU 9472867	A1	19941201	AU 1994-72867	19940908
AU 672520	B2	19961003		
AU 708219	B2	19990729	AU 1997-10013	19970103
AU 9710013	A1	19970313		
CN 1235825	A	19991124	CN 1999-106439	19990424
CN 1258501	A	20000705	CN 1999-106440	19990424
FI 9901970	A	19990916	FI 1999-1970	19990916

PRIORITY APPLN. INFO.:

AU 1991-5490	A	19910405
AU 1991-8394	A	19910916
EP 1992-302997	A3	19920403
HU 1992-1135	A	19920403
IL 1992-101491	A3	19920403
US 1992-863898	A3	19920406

AB A sustained-release capsule, adapted to be inserted into the rumen and retained within the rumen to continuously deliver a biol.-active compn., comprises an elongated tubular body comprising a tube and an end cap, for enclosing the biol.-active compn. The other end of the capsule is a, delivery end. The body has an opening at the delivery end of the capsule for delivery of the compn. to the rumen, and retention arms attached to, or formed integrally, with the cap. The arms are adapted to extend outwardly from the cap for retaining the capsule in the rumen. The arms are resilient to enable them to bend from their outwardly extending positions toward the body so that they lie alongside the body allowing the capsule to be inserted through the animal's esophagus. The resilient arms, normally extend from the body at an angle between 75.degree. and 90.degree. with respect to the axis of the tubular body. For each arm the cap has an external curved surface disposed with respect to the arm so that when the arm is bent toward the body it contacts the curved surface and the curved surface controls the bending of the arm so that the arm does not bend abruptly. The arms are adapted to return to their outwardly

extending positions when the capsule reaches the rumen. The cap is secured to one end by .gtoreq.2 circumferential beads having .gtoreq.1 sealing ring located inbetween. The biol.-active compn. comprises a polyether antibiotic, a glycopeptide antibiotic, an anthelmintic and/or an ectoparasiticide. Different sustained-release formulations are provided.

IC ICM A61K009-00
ICS A23K001-17; A23K001-00
CC 63-6 (Pharmaceuticals)
ST **sustained release** drug capsule rumen
IT Anthelmintics
Antibiotics
(**sustained-release** capsules contg., for delivery into the rumen)
IT Stomach, ruminant
(**sustained-release** delivery system for)
IT Parasiticides
(ecto-, **sustained-release** capsules contg., for delivery into the rumen)
IT Pharmaceutical dosage forms
(**sustained-release**, for delivery to the rumen)
IT 50-65-7, Niclosamide 51-17-2, Benzimidazole 54-05-7, Chloroquine 61-57-4, Niridazole 67-72-1, Hexachloroethane 69-05-6, Quinacrine hydrochloride 75-15-0, Carbon disulfide, biological studies 92-84-2, Phenothiazine 97-18-7, Bithionol 97-23-4, Dichlorophen 127-18-4, Tetrachloroethylene, biological studies 136-77-6, Hexylresorcinol 144-29-6, Piperazine citrate 148-79-8, Thiabendazole 548-57-2, Lucanthone hydrochloride 1404-55-3, Ristocetin 1404-90-6, Vancomycin 1642-54-2, Diethylcarbamazine citrate 1986-66-9, Stibocaptate 3546-41-6, Pyrvinium pamoate 3818-50-6, Bephenium hydroxy naphthoate 11054-70-9, Lasalocid 12750-79-7, Antibiotic A204 14433-82-0, Sodium thiacetarsamide 14769-73-4, Levamisole 15489-16-4, Stibophen 17090-79-8, Monensin 22204-24-6, Pyrantel pamoate 23255-93-8, Hycanthone mesylate 28300-74-5, Antimony potassium tartrate 28380-24-7, Nigericin 31357-58-1, Grisorixin 31431-39-7, Mebendazole 35865-33-9, Dianemycin 36505-48-3, Antibiotic X206 37305-75-2, Actaplanin 37332-99-3, Avoparcin 39434-32-7, A477 51257-84-2, Lenoremycin 52665-69-7, Antibiotic A23187 53003-10-4, Salinomycin 53026-37-2, Antibiotic A32887 54156-67-1, Isolasalocid A 54927-63-8, Septamycin 55134-13-9, Narasin 55898-33-4, Lysocellin 56092-81-0, Ionomycin 56283-74-0, Laidlomycin 57760-36-8, Alborixin 59149-05-2, Etheromycin 62618-08-0, Mutalomycin 67299-00-7, Antibiotic A 35512 70726-39-5, CP 47224 **73989-17-0, Avermectin** 75139-06-9, Tetronasin 75217-55-9, Antibiotic X-14766A 84331-31-7 145323-81-5
RL: BIOL (Biological study)
(**sustained-release** capsules contg., for delivery into the rumen)
IT **73989-17-0, Avermectin**
RL: BIOL (Biological study)
(**sustained-release** capsules contg., for delivery into the rumen)
RN 73989-17-0 HCAPLUS
CN Avermectin (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L32 ANSWER 18 OF 20 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1992:433690 HCAPLUS
DOCUMENT NUMBER: 117:33690
TITLE: Bioerodible pharmaceutical **implants**
INVENTOR(S): Shih, Chung; Sparer, Randall V.; Zentner, Gaylen M.; Seward, Randolph Lee
PATENT ASSIGNEE(S): Merck and Co., Inc., USA
SOURCE: Eur. Pat. Appl., 16 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 473223	A1	19920304	EP 1991-202084	19910815
EP 473223	B1	19950510		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
IL 99180	A1	19980104	IL 1991-99180	19910814
AT 122230	E	19950515	AT 1991-202084	19910815
ES 2072530	T3	19950716	ES 1991-202084	19910815
AU 9182678	A1	19920227	AU 1991-82678	19910821
AU 645594	B2	19940120		
JP 04230621	A2	19920819	JP 1991-209024	19910821
JP 2588328	B2	19970305		
CA 2049668	AA	19920223	CA 1991-2049668	19910822
US 5837228	A	19981117	US 1992-939539	19920902
PRIORITY APPLN. INFO.:			US 1990-570742	19900822

AB A bioerodible controlled-release dosage form comprises a poly(ortho ester) or a polyacetal wherein the polymer is formed from the condensation of (1) a deketene acetal or a divinyl ether, (2) a beneficial agent having OH functional groups, and (3) polyols. Thus, a mixt. contg. tetraethylene glycol, 1,6-hexanediol, BHT, 1,2,6-hexanetriol, MgO, ivermectin, and 3,9-bis-(ethylidene)-2,4,8,10-tetraoxaspiro[5,5]-undecane was dispensed into a FEP teflon tubing (0.73 mm inner diam.) and cured at 60.degree. to give a poly(ortho ester) **implant** contg. 21.4 % ivermectin. The in vitro ivermectin release rate in a pH 5.0 medium was 22.1 %/h and when the product was s.c. **implanted** in beagle dogs, it demonstrated the efficacy against challenges of heartworm larvae even after 9 mo.
IC ICM A61K009-58
ICS A61K047-48
CC 63-6 (Pharmaceuticals)
ST bioerodible polyortho ester drug **implant**; polyacetal bioerodible drug **implant**; ivermectin polyortho ester **implant**
IT Polyoxymethylenes, biological studies
RL: BIOL (Biological study)
(bioerodible pharmaceutical **implant** manuf. with)
IT Adrenergic agonists
Adrenergic antagonists
Anthelmintics
Antibiotics
Anticholesteremics and Hypolipemics
Anticoagulants and Antithrombotics
Antihistaminics

Antihypertensives
Fungicides and Fungistats
Hypnotics and Sedatives
Inflammation inhibitors
Narcotic antagonists
Narcotics
Neoplasm inhibitors
Nervous system agents
Nervous system stimulants
Virucides and Virustats
Steroids, biological studies
Vitamins
RL: PREP (Preparation)
(bioerodible polymers prepn. from diketene acetals and polyols and, for **implantation**)

IT Parkinsonism
(inhibitors for, bioerodible polymers prepn. from diketene acetals and polyols and, for **implantation**)

IT Vasodilators
(coronary, bioerodible polymers prepn. from diketene acetals and polyols and, for **implantation**)

IT Pharmaceutical dosage forms
(**implants**, bioerodible poly(ortho esters) and polyacetals for)

IT Polyethers, biological studies
RL: BIOL (Biological study)
(ortho esters, bioerodible pharmaceutical **implant** manuf. with)

IT Animal growth regulators
RL: PREP (Preparation)
(promoters, bioerodible polymers prepn. from diketene acetals and polyols and, for **implantation**)

IT **51570-36-6D, Milbemycin**, oximes, reaction products with polyols and diketene acetals **51570-36-6D, Milbemycin**, reaction products with polyols and diketene acetals 70288-86-7D, Ivermectin, reaction products with polyols and diketene acetals **73989-17-0D, Avermectin**, reaction products with polyols and diketene acetals 102130-84-7D, Nemadectin, reaction products with polyols and diketene acetals 113507-06-5D, Moxidectin, reaction products with polyols and diketene acetals
RL: BIOL (Biological study)
(bioerodible pharmaceutical **implant** manuf. with)

IT 142114-19-0P
RL: PREP (Preparation)
(prepn. of, for bioerodible **implantation**)

IT **51570-36-6D, Milbemycin**, oximes, reaction products with polyols and diketene acetals **73989-17-0D, Avermectin**, reaction products with polyols and diketene acetals
RL: BIOL (Biological study)
(bioerodible pharmaceutical **implant** manuf. with)

RN 51570-36-6 HCAPLUS
CN Milbemycin (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 73989-17-0 HCAPLUS

CN Avermectin (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L32 ANSWER 19 OF 20 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1987:541112 HCAPLUS
DOCUMENT NUMBER: 107:141112
TITLE: Dispenser for the **sustained release** of pharmaceuticals
INVENTOR(S): Eckenhoff, James B.; Cortese, Richard; Landrau, Felix A.
PATENT ASSIGNEE(S): Alza Corp., USA
SOURCE: Ger. Offen., 15 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 3626103	A1	19870212	DE 1986-3626103	19860801
DE 3626103	C2	19980219		
US 4684524	A	19870804	US 1985-763493	19850808
ES 556303	A1	19871016	ES 1986-556303	19860619
ES 556375	A1	19880401	ES 1986-556375	19860620
GB 2178659	A1	19870218	GB 1986-18350	19860728
GB 2178659	B2	19890913		
JP 62039518	A2	19870220	JP 1986-178598	19860729
JP 08018972	B4	19960228		
GB 2178660	A1	19870218	GB 1986-18568	19860730
GB 2178660	B2	19890906		
DE 3625915	A1	19870219	DE 1986-3625915	19860731
DE 3625915	C2	19970424		
JP 62039519	A2	19870220	JP 1986-181189	19860731
JP 07059497	B4	19950628		
AU 8660780	A1	19870212	AU 1986-60780	19860801
AU 590308	B2	19891102		
FR 2585950	A1	19870213	FR 1986-11370	19860806
FR 2585950	B1	19890303		
FR 2585951	A1	19870213	FR 1986-11371	19860806
FR 2585951	B1	19890303		
BR 8603756	A	19870310	BR 1986-3756	19860806
ZA 8605914	A	19870429	ZA 1986-5914	19860806
CA 1265966	A1	19900220	CA 1986-515469	19860807
ZA 8605982	A	19870429	ZA 1986-5982	19860808
AU 654515	B2	19941110	AU 1991-89738	19911216

PRIORITY APPLN. INFO.: US 1985-763493 19850808
US 1984-590778 19840319
US 1985-764143 19850809

AB The title dispenser, such as a capsule, has a perforated wall and contains an active ingredient, a material m. at body temp. and an osmotically-active sol. compd. The chamber of a capsule contained a mass made of tetracycline-HCl 1000, polyethylene glycol 600 650, polyethylene glycol 1000 335, sorbitan monostearate 1.2, and 2,6-di-tert-butylcresol 0.02 mg, as well as a NaCl tablet placed on top of the mass. The wall was

made of 90% cellulose acetate butyrate and 10% polyethylene glycol 400.
IC ICM B01J004-04
ICS A61K009-22; A61K009-52; A61K031-415; A61K031-425; A61K031-47; A61K031-505; A61K031-365; A61K031-35; A61K031-545; A61K031-18; A61K031-56
ICA A61K031-475; A61K031-54; A61K031-17; A61K031-16; A61K031-65; A61K031-405; A61K031-56; A61K031-045
CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 18
ST **sustained release** drug dispenser
IT Mineral elements
Trace elements, biological studies
Vitamins
RL: BIOL (Biological study)
(pharmaceutical dispensers for, **sustained-release**)
IT Pharmaceutical dosage forms
(**sustained-release**, dispensers for)
IT 50-02-2 53-86-1, Indomethacin 56-75-7, Chloramphenicol 57-68-1 64-75-5, Tetracycline hydrochloride 68-26-8, Vitamin A 72-14-0, Sulfathiazole 1314-13-2, Zinc oxide, biological studies 1344-70-3, Copper oxide 1406-16-2, Vitamin D 1406-18-4, Vitamin E 2135-17-3 7439-95-4, Magnesium, biological studies 7439-96-5, Manganese, biological studies 7440-48-4, Cobalt, biological studies 7440-50-8, Copper, biological studies 7440-66-6, Zinc, biological studies 7487-88-9, Magnesium sulfate, biological studies 7681-11-0, Potassium iodide, biological studies 7733-02-0, Zinc sulfate 7782-49-2, Selenium, biological studies 10124-55-7, Manganese sulfate 10393-49-4 11111-12-9, Cephalosporin 14013-56-0 14769-73-4, Levamisole 15686-83-6, Pyrantel 16595-80-5 20461-54-5, Iodide, biological studies
20574-50-9, Morantel 31431-39-7, Mebendazole 53716-50-0 55268-74-1, Praziquantel 70288-86-7, Ivermectin **73989-17-0**, **Avermectin**
RL: BIOL (Biological study)
(**sustained-release** dispenser for)
IT **73989-17-0, Avermectin**
RL: BIOL (Biological study)
(**sustained-release** dispenser for)
RN 73989-17-0 HCAPLUS
CN Avermectin (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L32 ANSWER 20 OF 20 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1987:201740 HCAPLUS
DOCUMENT NUMBER: 106:201740
TITLE: Delivery device for release of an active ingredient in
ruminants
INVENTOR(S): Eckenhoff, James B.
PATENT ASSIGNEE(S): Alza Corp., USA
SOURCE: Ger. Offen., 12 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 3626362	A1	19870219	DE 1986-3626362	19860804
DE 3626362	C2	19960919		
US 4704118	A	19871103	US 1985-766456	19850816
GB 2178956	A1	19870225	GB 1986-18805	19860801
GB 2178956	B2	19890906		
NL 8601993	A	19870316	NL 1986-1993	19860804
AU 8660880	A1	19870219	AU 1986-60880	19860805
AU 585044	B2	19890608		
FR 2586188	A1	19870220	FR 1986-11372	19860806
FR 2586188	B1	19890901		
CA 1252362	A1	19890411	CA 1986-515467	19860807
ZA 8606013	A	19870325	ZA 1986-6013	19860811
US 4871544	A	19891003	US 1987-126460	19871127
US 4883667	A	19891128	US 1987-126079	19871127
US 4966767	A	19901030	US 1989-327935	19890323
US 4955881	A	19900911	US 1989-384613	19890725
US 5098425	A	19920324	US 1990-538953	19900615

PRIORITY APPLN. INFO.:
US 1985-766456 19850816
US 1987-42197 19870424
US 1987-126460 19871127

AB A delivery device for controlled release of an active ingredient (e.g. pharmaceutical) in ruminants consists of a capsule-like container which encloses the active ingredient, a carrier which releases the active ingredient at .gtoreq.24.degree., an expandable compd., and a wt.-increasing (d. > 1.0) compd. to balance the d. of the expandable compd. Release of 0.5 mg ivermectin/h for 480 h in warm media was achieved by filling a gelatin capsule with ivermectin 13.98, Butronic L-1 polyol 193, NaCl 1.2, Carbopol 934-p 4.6 and Fe filings 30g and coating the capsule with a cellulose acetate butyrate-polyethylene glycol 400 (91:9) layer.

IC ICM A61K009-00
ICS B01J004-04; A61K009-48; A61K009-52; A61J003-00; A61D007-00; A61K031-41; A61K031-425; A61K031-415; A61K031-505; A61K031-545; A61K031-18

ICA A61D007-00; A61K031-43; A61K031-65; A61K031-74; A61K037-24

CC 63-6 (Pharmaceuticals)

ST ruminant **controlled release** capsule drug nutrient

IT Vinyl compounds, polymers
RL: BIOL (Biological study)
(carboxy-, **controlled-release** pharmaceutical capsules contg., for ruminants)

IT Ruminant
(**controlled-release** pharmaceutical and nutritional capsules for)

IT Fatty acids, esters
RL: BIOL (Biological study)
(**controlled-release** pharmaceutical capsule contg., for ruminants)

IT Beeswax
Acrylic polymers, biological studies
Cocoa butter
Cocoa butter
Fats, biological studies
Glycerides, biological studies

Paraffin waxes and Hydrocarbon waxes, biological studies
Polysaccharides, biological studies
Waxes and Waxy substances
RL: BIOL (Biological study)
(**controlled-release** pharmaceutical capsules contg., for ruminants)

IT Gelatins, biological studies
RL: BIOL (Biological study)
(**controlled-release** pharmaceutical devices contg., for ruminants)

IT Pharmaceutical dosage forms
(capsules, **controlled-release**, for ruminants, manuf. of and formulations for)

IT 7439-89-6, Iron, biological studies 9003-05-8, Polyacrylamide 12597-69-2, Steel, biological studies 56300-07-3 25322-68-3, Polyethylene oxide
RL: BIOL (Biological study)
(**controlled-release** pharmaceutical capsule contg., for ruminants)

IT 50-02-2 57-68-1 59-51-8 72-14-0 75-21-8, Ethylene oxide, biological studies 106-88-7, 1,2-Butylene oxide 657-27-2 1323-39-3, Propylene glycol monostearate 2135-17-3 6182-11-2, Propylene glycol distearate 7439-95-4, Magnesium, biological studies 7647-14-5, Sodium chloride, biological studies 9004-99-3, Polyethylene glycol monostearate 11104-61-3, Cobalt oxide 11111-12-9, Cephalosporin 14255-87-9, Parbendazole 14769-73-4, Levamisole 15686-83-6 20574-50-9, Morantel 25053-81-0, Ethylene glycol monomethacrylate-ethylene glycol dimethacrylate copolymer 31431-39-7, Mebendazole 53716-50-0, Oxfendazole 55268-74-1 57916-92-4, Carbopol 934 P 70288-86-7, Ivermectin **73989-17-0, Avermectin** 107628-12-6
RL: BIOL (Biological study)
(**controlled-release** pharmaceutical capsules contg., for ruminants)

IT 7440-48-4, Cobalt, biological studies
RL: BIOL (Biological study)
(mixt. with iron, **controlled-release** pharmaceutical capsules contg., for ruminants)

IT 9004-35-7, Cellulose acetate 9004-36-8, Cellulose acetate butyrate 9004-38-0, Cellulose acetate phthalate 70726-37-3, Cellulose propionate morpholinobutyrate 108340-51-8
RL: BIOL (Biological study)
(pharmaceutical capsules coating with, for **controlled release**)

IT **73989-17-0, Avermectin**
RL: BIOL (Biological study)
(**controlled-release** pharmaceutical capsules contg., for ruminants)

RN 73989-17-0 HCAPLUS
CN Avermectin (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

=> fil uspatfull

FILE 'USPATFULL' ENTERED AT 12:21:17 ON 13 AUG 2001

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L51         176 S L50 AND L49 AND L45 AND L44 AND L43
L52           0 S L51 AND L37
L53          35 S L41
L54          29 S L41 AND (L50 OR L49 OR L45 OR L44 OR L43)
L55          29 S L40 AND (L50 OR L49 OR L45 OR L44 OR L43)
L56          25 S L55 NOT L42
L57       28004 S IMPLANT?/AB,TI,CLM
L58           0 S L56 AND L57

     FILE 'HCAPLUS' ENTERED AT 12:17:01 ON 13 AUG 2001

     FILE 'USPATFULL' ENTERED AT 12:21:17 ON 13 AUG 2001
L59           6 S L37 AND L57
L60           8 S L42 OR L59

=> d bib ab hit 1-8 160


L60  ANSWER 1 OF 8  USPATFULL
AN     2000:167979  USPATFULL
TI     Endoparasiticidal compositions
IN     Mencke, Norbert, Leverkusen, Germany, Federal Republic of
       Harder, Achim, Koln, Germany, Federal Republic of
       Jeschke, Peter, Leverkusen, Germany, Federal Republic of
       Kolbl, Barbara, Koln, Germany, Federal Republic of
PA     Bayer Aktiengesellschaft, Leverkusen, Germany, Federal Republic of
       (non-U.S. corporation)
PI     US 6159932              20001212
       WO 9638165  19961205
AI     US 1997-952356          19971119 (8)
       WO 1996-EP2170          19960520
                               19971119  PCT 371 date
                               19971119  PCT 102(e) date
PRAI   DE 1995-19520275    19950602
DT     Utility
FS     Granted
EXNAM  Primary Examiner: Weddington, Kevin E.
LREP   Gil, Joseph C., Akorli, Godfried R.
CLMN   Number of Claims: 20
ECL    Exemplary Claim: 1
DRWN   No Drawings
LN.CNT 834
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB     The present invention relates to mixtures of avermectins,
       22,23-dihydroavermectins B.sub.1 (ivermectins) and milbemycins
       from the class of the macrocyclic lactones in combination with cyclic
       depsipeptides, optionally in the presence of praziquantel or
       epsiprantel, for increasing the endoparasiticidal action in
       endoparasiticidal compositions.
AB     The present invention relates to mixtures of avermectins,
       22,23-dihydroavermectins B.sub.1 (ivermectins) and milbemycins
       from the class of the macrocyclic lactones in combination with cyclic
       depsipeptides, optionally in the presence of praziquantel or
       epsiprantel, for increasing the endoparasiticidal action in
       endoparasiticidal compositions.
SUMM   The active substances are administered, either directly or in the form
       of suitable preparations, enterally, parenterally, dermally, nasally,
by
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treating the environment or with the aid of shaped articles containing the active substance, such as, for example, strips, plates, tapes, neck bands, **ear** tags, limb bands or marking devices.

SUMM Enteral administration of the active substances is effected, for example, orally in the form of powders, tablets, capsules, pastes, drinks, granules, solutions which can be applied orally, suspensions and emulsions, boli, medicated feed or drinking water. Dermal application is effected, for example, in the form of dipping, spraying, or pouring-on and spotting-on. Parenteral administration is effected, for example, in the form of injection (intramuscular, subcutaneous, intravenous or intraperitoneal) or by **implants**.

CLM What is claimed is:

1. Synergistic endoparasiticidal compositions which comprise at least one **avermectin**, 22,23-dihydroavermectin B.sub.1 (ivermectins) or **milbemycin** from the class of the macrocyclic lactones in combonation with cyclic depsipeptides consisting of amino acids and hydroxycarboxylic acids as ring structural units and 6 to 30 ring atoms, optionally in the presence of praziquantel or epsiprantel.

8. Endoparasiticidal compositions according to claim 1 for **cattle**, horses, **sheep**, pigs, goats, camels, water buffaloes, donkeys, rabbits, fallow deer, reindeer, mink, chinchilla, raccoon, birds, fish, reptiles and insects, wherein the weight ratio of macrocyclic lactone to depsipeptide is 1:20 to 4000.

12. Endoparasiticidal compositions according to any one of claim 1 characterized in that the **avermectins** are selected from the B.sub.1 series B.sub.1a and B.sub.1b.

13. Endoparasiticidal compositions according to any one of claim 1 characterized in that the macrocyclic lactones are selected from **doramectin** and moxidectin.

IT **51570-36-6**, Milbemycin 55268-74-1, Praziquantel 70209-81-3, Ivermectin B1b 70288-86-7, Ivermectin 71827-03-7, Ivermectin B1a **73989-17-0**, Avermectin 98123-83-2, Epsiprantel 133413-70-4, PF 1022A
(endoparasitic drug combination)

L60 ANSWER 2 OF 8 USPATFULL
AN 1998:143639 USPATFULL
TI Bioerodible **implants**
IN Shih, Chung, Lawrence, KS, United States
Zentner, Gaylen M., Lawrence, KS, United States
Sparer, Randall V., Lawrence, KS, United States
Seward, R. Lee, Watchung, NJ, United States
PA Merck & Co., Inc., Rahway, NJ, United States (U.S. corporation)
PI US 5837228 19981117
AI US 1992-939539 19920902 (7)
RLI Continuation of Ser. No. US 1990-570742, filed on 22 Aug 1990, now abandoned
DT Utility

FS Granted
EXNAM Primary Examiner: Page, Thurman K.; Assistant Examiner: Azpuru, C.
LREP Bigley, Francis F., Daniel, Mark R., DiPrima, Joseph F.
CLMN Number of Claims: 18
ECL Exemplary Claim: 1
DRWN 3 Drawing Figure(s); 3 Drawing Page(s)
LN.CNT 633
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A bioerodible controlled release dosage form is disclosed comprising a polymer formed by condensing beneficial agents having a hydroxyl functionality of two or more with diketene acetals or divinyl ethers which delivers beneficial agents to a biological environment of use. A statistically significant portion of the beneficial agent is covalently bonded within the polymer matrix.
TI Bioerodible **implants**
DRWD FIG. 1 depicts a rod-shaped **implant** manufactured in accordance with the present invention.
DRWD FIG. 2 plots tensile modulus, weight percentage of beneficial agent and dissolution rate for **implants** made in accordance with the present invention.
DRWD FIG. 3 plots glass transition temperature, tensile strength, weight percent of beneficial agent, and dissolution lag-time for **implants** made in accordance with the present invention.
DETD The instant invention may be shaped in numerous geometric configurations. A rod-shaped device, 1, is illustrated in FIG. 1. When sized at 0.5 mm to 5 mm diameter and 0.5 to 10 cm in length this shape is readily suited for **implantation**, although larger and smaller dimensions are within the scope of the invention. The beneficial agent (frequently a drug), 2, is to a substantial degree covalently incorporated into the backbone of the polymer chains comprising the bioerodible matrix, 3, with a portion of the total drug also dispersed throughout the matrix. Other additives, 4, such as stabilizers, antioxidants and catalysts may be optionally included. The bioerodible controlled release dosage form is **implanted** intramuscularly, subcutaneously or intraperitoneally. If desired, more than one **implant** may be inserted.
DETD In a preferred embodiment, a poly(ortho ester) **implant** is synthesized by a condensation reaction of polyol monomers, including the polyol anthelmintic drug ivermectin, with a diketene acetal to form a potent **implantable** dosage form useful against various developmental stages of Dirofilaria immitis, a filarial parasite and causative organism of canine heartworm disease. Specifically, ivermectin and various combinations of other polyols such as 1,6-hexanediol, 1,7-heptanediol, tetraethylene glycol, triethylene glycol, and 1,2,6-hexanetriol were covalently reacted with the diketene acetal 3,9-bis-(ethylidene)-2,4,8,10-tetraoxaspiro[5,5]undecane (viz., DETOSU) to form a poly(ortho ester) matrix. Ivermectin is a polyol with three hydroxyl groups, and therefore reacts with the DETOSU. A significant portion (20 to 60%) of the ivermectin was covalently incorporated into the poly(ortho ester) chains. This dosage form provides prophylactic levels of ivermectin for periods ranging from three to fifteen months with a single dose. This dosage form can be administered to a recipient by simple subcutaneous injection. This **implant** is biodegradable and completely erodes within the animal while releasing

drug, thus ensuring that accumulation of **implants** is minimized with repeat dosings.

DETD The avermectin and milbemycin compounds described in the above references, and which may be incorporated as a beneficial agent in the **implant** of the present invention, are particularly effective against endo or ecto parasites, of animals and man, that feed on or are associated with blood, body secretions or tissues, such as developing larvae of Dirofilaria immitis in dogs and cats. Other endoparasites of dogs and cats particularly hookworms, Ancylostoma caninum, Ancyclostoma tubaeforma, Ancylostoma braziliense, and Uncinaria stenocephala, and whipworms Trichuris vulpis are likely targets. Ascarids, such as Toxocara canis, Toxocara cati, and Toxascaris leonina, are also potential targets, as are the threadworms Strongyloides stercoralis and lungworms Capillaria sp. and Aelurostrongylus sp. Ecto parasites particularly **ear** mites otodectes cynotis, other mites, fleas and ticks may also be affected.

DETD The **implant** can be synthesized and fabricated as either a linear polymer or crosslinked polymer erodible matrix. The techniques used in fabricating the **implant** will vary. Linear (thermoplastic) polymers can be synthesized and then reheated at a later time for compounding with additives (e.g., stabilizers and antioxidants). This mixture can then be reheated at a later time for molding into the final shape. When processing a crosslinked polymer **implant**, all monomers (including the beneficial agent) and additives are added to the polymerization reaction prior to complete polymerization. Since crosslinking agent(s) is/are present, the mixture cannot be easily molded once the polymerization reaction is completed. It is preferred that the **implant** be shaped and molded prior to complete cure. Both continuous and batch processing procedures are applicable.

DETD Ivermectin/Poly(Ortho Ester) **Implants**

DETD Ivermectin has been incorporated into a crosslinked poly(ortho ester) erodible polymer and utilized as an **implant** for the control of parasites. The **implant** is manufactured in three stages: 1) Synthesis of a partially polymerized poly(ortho ester) paste containing the homogeneously mixed additives; 2) Dispensing of the paste into rod-shaped molds; and, 3) Curing and removal of the completely polymerized rods from the molds. The poly(ortho ester) was a condensation polymer comprised of two fundamental types of monomers: polyols (e.g., 1,6-hexanediol, tetraethylene glycol, 1,2,6-hexanetriol, ivermectin) and a diketene acetal (e.g., DETOSU). It is known that ortho ester bonds are substantially more stable to hydrolysis under basic pH conditions. The addition of an ortho ester bond stabilizer such as MgO or Mg(OH).sub.2 which results in an alkaline pH, substantially modified (slowed) the erosion process. In this invention, the beneficial agent (ivermectin) of a preferred embodiment was also a polyol and reacted as a monomer with the DETOSU to become covalently bonded within the poly(ortho ester) backbone. A statistically significant portion (1 to 100%) of the total drug covalently bonded within the polymer backbone is within the scope of the invention, with typical values of 20 to 60% bonded. This provides the advantage that the bonded ivermectin cannot diffuse out of the dosage form until it is hydrolytically cleaved from the crosslinked poly(ortho ester).

DETD The thermal, mechanical and drug release performance of the poly(ortho

ester)/ivermectin **implant** was controlled by the amounts of DETOSU, stabilizer, and ivermectin, and the amounts and types of polyols (diols and crosslinkers) in the formulation. Suitable polyols, stabilizers, and polymerization stoichiometries are as follows:

DETD Condensation polymerizations require pure monomers to maximize polymer molecular weights. The monomers used to fabricate the **implant** are polyfunctional. If there are monofunctional impurities in the reagents, the polymerization will be prematurely terminated and the erosion rate of the poly(ortho ester) may be altered. Monomers with purities .gtoreq.90% are desired and monomers of purity .gtoreq.98% are generally preferred.

DETD It is preferred that the ivermectin/poly (ortho ester) crosslinked **implant** be synthesized by a batch fabrication process where the ivermectin is present during the bulk polymerization reaction. This will allow the ivermectin to be covalently incorporated into the poly(ortho ester) backbone. Example 1 describes the synthesis of such an **implant**. The stoichiometry of the reaction was within the preferred range of 0.7 to 1.2. The polyols (tetraethylene glycol, 1,6-hexanediol, and 1,2,6-hexanetriol), ivermectin, stabilizer (MgO) and antioxidant (BHT, if present) were pre-mixed. The DETOSU (diketene acetal) was then added to begin the polymerization reaction. The MgO is not soluble in this mixture. During this reaction/mixing step, the polymer simultaneously increased in molecular weight and degree of crosslinking. The resulting paste must not be completely polymerized or it will be too viscous (>2,000,000 cp) to extrude into the preferred molds. However, if the mixture is <2,000 cp the insoluble MgO stabilizer may settle out during cure. This could produce **implants** with irreproducible erosion. Typically, a viscosity of 5,000 to 50,000 cp (20.degree. C.; 10 sec.sup.-1) resulted in good suspension and uniformity of the MgO and permitted room temperature molding. This viscous reaction mixture was dispensed into molds to form the **implant** rods. A preferred mold is fluorinated hydrocarbon polymeric tubing (FEP tubing 1.6 mm o.d., 0.7 to 0.9 mm i.d.). The dispenser was a stainless steel piston and cylinder which, when loaded with the paste was hydraulically pressurized to force the paste into the mold tubes attached to the bottom of the cylinder. The filled tubes were cured in a low humidity environment at a controlled elevated temperature to complete the polymerization. The cured rods were removed from the tubes and cut to the proper length prior to packaging.

DETD An Atlantic Research 2CV Helicone Mixer was heated to 60.degree. C. in a low humidity room (approximately 70.degree. F. and 5% RH). Tetraethylene glycol (5.5702 gm), 1,6-hexanediol (3.3899 gm), 1,2,6-hexanetriol (2.0437 gm), magnesium oxide (0.8957 gm), and ivermectin (7.1997 gm, pre-dried under vacuum to reduce residual solvents) were added to the mixer and stirred for 1 minute. DETOSU (16.9229 gm) was added as a liquid to the mixture and was stirred at a moderate speed (setting "6") for 60 minutes at which time the mixture had a viscosity of 16,600 cp (20.degree. C.; 10 sec.sup.-1). It was dispensed into FEP teflon tubing

and cured for 22.5 hours at 60.degree. C. The poly(ortho ester) **implants** were removed from the tubing after cooling to room temperature. The **implants** contained 19.5.+-.0.09 wt % total ivermectin by content, and 46.8%.+-.0.84 of that was bound to the polymer matrix.

DETD An Atlantic Research 2CV Helicone Mixer was heated to 60.degree. C. in a low humidity room (approximately 70.degree. F. and 5% RH). Tetraethylene glycol (3.7141 gm), 1,6-hexanediol (2.2603 gm), 1,2,6-hexanetriol (1.3696 gm) and magnesium oxide (0.6049 gm) were added to the mixer and stirred for 1 minute. DETOSU (11.3344 gm) was added as a liquid to the mixture and was stirred at a moderate speed (setting "6") for 45 minutes. Ivermectin (4.7963 gm, pre-dried under vacuum to reduce residual solvents) was then added and mixed for 45 minutes at 40.degree. C. at which time the mixture had a viscosity of 16,900 cp (20.degree. C.; 10 sec.sup.-1), It was dispensed into PEP teflon tubing and cured for 18.5 hours at 60.degree. C. The poly(ortho ester) **implants** were removed from the tubing after cooling to room temperature. The **implants** contained 18.8.+-.0.07 wt % total ivermectin by content, and 38.4%.+-.3.16 of that was bound to the polymer matrix.

DETD An Atlantic Research 2CV Helicone Mixer was heated to 50.degree. C. in a low humidity room (approximately 70.degree. C. and 5% RH). Tetraethylene glycol (5.5637 gm), 1,6-hexanediol (3.3848 gm) and DETOSU (5.0397 gm) were reacted to form a prepolymer predominantly containing hydroxyl end groups. Mixing proceeded for 60 minutes at a moderate speed (setting "4"). Ivermectin (7.1877 gm, pre-dried under vacuum to reduce residual solvents), 1,2,6-hexanetriol (2.0356 gm) and magnesium oxide (0.8986 gm) were added to the mixer and stirred at a fast speed (setting "9") at 35.degree. C. for 15 minutes. The balance of the DETOSU (11.8118 gm) was added as a liquid to the mixture and stirred at a moderate speed (setting "4") for 15 minutes at 35.degree. C. at which time the mixture had a viscosity of 20,100 cp (20.degree. C.; 10 sec.sup.-1). It was dispensed into FEP teflon tubing and cured for 22 hours at 60.degree. C. The poly(ortho ester) **implants** were removed from the tubing after cooling to room temperature. The **implants** contained 18.0.+-.0.11 wt % total ivermectin by content, and 60.5%.+-.4.29 of that was bound to the polymer matrix.

DETD An Atlantic Research 2CV Helicone Mixer was heated to 35.degree. C. in a low humidity room (approximately 70.degree. F. and 5% RH). Tetraethylene glycol (3.9264 gm), 1,6-hexanediol (2.3887 gm) and DETOSU (11.9329 gm) were reacted to form a prepolymer predominantly containing ketene acetal end groups. Mixing proceeded for 1 minute at a moderate speed (setting "4"), and then magnesium oxide (0.6343 gm) was added and mixed for 9 minutes more. Ivermectin (5.0630 gm, pre-dried under vacuum to reduce residual solvents) was added to the mixer and stirred at a fast speed (setting "9") at 35.degree. C. for 10 minutes. The 1,2,6-hexanetriol

crosslinker (1.4634 gm) was added and mixing at the fast speed continued for 10 minutes at which time the mixture had a viscosity of 13,900 cp (20.degree. C.; 10 sec.sup.-1). It was dispensed into FEP teflon tubing and cured for 22 hours at 60.degree. C. The poly(ortho ester) **implants** were removed from the tubing after cooling to room temperature. The **implants** contained 17.5.+-.0.14 wt % total ivermectin by content, and 35.3%.+-.1.62 of that was bound to the polymer matrix.

DETD This example describes the manufacture and in vitro/in vivo testing of an ivermectin/poly(ortho ester) **implant** formulated to protect dogs from D. immitis heartworm infestation for up to 6 months.

DETD An Atlantic Research 2CV Helicone Mixer was heated to 50.degree. C. in an enclosed working area (approximately 70.degree. F./30% RH). Tetraethylene glycol (15.5944 gm), 1,6-hexanediol (9.4881 gm), BHT (0.0203 gm), 1,2,6-hexanetriol (5.7562 gm), magnesium oxide (2.5025 gm), and ivermectin (20.0176 gm, pre-dried under vacuum to reduce residual solvents) were added to the mixer and stirred for 1 minute. DETOSU (46.7429 gm) was added as a liquid to the mixture and was stirred at a moderate speed for 60 minutes. The mixture was dispensed into FEP teflon tubing (0.73 mm I.D.) and cured for 19.5 hours at 60.degree. C. The poly(ortho ester) **implants** were removed from the tubing after cooling to room temperature. The **implants** contained 21.4 wt %.+-.0.21 total ivermectin by content, and 26.4%.+-.4.71 of that total was bound to the polymer matrix. Tensile testing with an Instron 1130 Tensile Tester at 5 cm/minute gave a Young's modulus of 155.6.+-.3.1 ksi and a tensile strength of 6.5.+-.0.3 ksi. The glass transition temperature was 43.1.+-.0.46.degree. C. as measured by thermomechanical analysis (Perkin Elmer TMA-7) at 100 mN, 10.degree. C./minute. A quality control in vitro dissolution test was performed at 37.degree. C. using the rotating bottle method (NE XIV) and a dissolution medium of 0.5M sodium chloride and 0.5M sodium acetate (adjusted to pH 5.0 with HCl) in 30% aqueous isopropanol. The in vitro ivermectin release rate was 22.1.+-.1.05%/hour and the lag time was 0.4.+-.0.13 hours. This batch was **implanted** subcutaneously in beagle dogs at a dose of 1 cm of **implant** for each 5 kg of dog weight and demonstrated efficacy against challenges of infective D. immitis heartworm larvae at the time of **implantation** and at 3 months, 6 months or 9 months post-**implantation** of a single **implanted** dosage form.

DETD Reproducible manufacture was demonstrated based on the physical properties and in vitro drug release performance of five batches of ivermectin/poly(ortho ester) **implants** fabricated according to the method in Example 5. Each batch was fabricated in a room at 70.degree. F. at relative humidities between 15% and 25%. FIGS. 3 and 4 show the similarities among the five batches in the tensile modulus, tensile strength, dissolution rate, dissolution lag-time, glass transition temperature, ivermectin loading, and % of ivermectin bound to the polymer.

DETD An ivermectin/poly(ortho ester) **implant** is prepared according to procedures outlined in Example 5 with the following reagents:

DETD An ivermectin/poly(ortho ester) **implant** is prepared according

to procedures outlined in Example 5 with the following reagents:
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DETD An ivermectin/poly(ortho ester) **implant** is prepared according to procedures outlined in Example 5 with the following reagents:
DETD An ivermectin/poly(ortho ester) **implant** is prepared according to procedures outlined in Example 5 with the following reagents:
CLM What is claimed is:
3. The dosage form of claim 2 wherein the beneficial agent is an anthelmintic selected from the group consisting of: a) **avermectins**; b) **milbemycins**.

5. The dosage form of claim 4 wherein the beneficial agent is selected from: a) ivermectin; b) moxidectin; c) nemadectin; d) **milbemycin** -5-oxime.

15. A method of treating a disease condition in a human or nonhuman **animal**, for those in need thereof, which comprises the **implantation** of a bioerodible controlled release device comprising a bioerodible polymer selected from a poly(orthoester) or a polyacetal in which a beneficial agent is covalently incorporated into a

chain backbone of the polymer, wherein the beneficial agent (a) is capable of being released from the polymer into the environment of use; and (b) has a hydroxyl functionality of at least two; and the total equivalents of hydroxyl are present in stoichiometric ratios of 1 equivalent of hydroxyl to 0.1 to 1.5 equivalents of ketene acetal or vinyl ether.

18. The method of claim 15 wherein the treatment is provided prophylactically to a human or nonhuman **animal**.

IT **51570-36-6D**, Milbemycin, oximes, reaction products with polyols and diketene acetals **51570-36-6D**, Milbemycin, reaction products with polyols and diketene acetals 70288-86-7D, Ivermectin, reaction products with polyols and diketene acetals **73989-17-0D**, Avermectin, reaction products with polyols and diketene acetals 102130-84-7D, Nemadectin, reaction products with polyols and diketene acetals 113507-06-5D, Moxidectin, reaction products with polyols and diketene acetals
(bioerodible pharmaceutical implant manuf. with)

L60 ANSWER 3 OF 8 USPATFULL
AN 1998:85201 USPATFULL
TI Method for automatic dosing of drugs
IN Jacobsen, Stephen C., Salt Lake City, UT, United States
Zentner, Gaylen M., Salt Lake City, UT, United States
PA Sarcos, Inc., Salt Lake City, UT, United States (U.S. corporation)
PI US 5782799 19980721
AI US 1997-797296 19970207 (8)
DT Utility
FS Granted
EXNAM Primary Examiner: Yasko, John D.
LREP Thorpe North & Western LLP
CLMN Number of Claims: 53

ECL Exemplary Claim: 1
DRWN 9 Drawing Figure(s); 8 Drawing Page(s)
LN.CNT 1011
AB The method for automatic dosing of drugs utilizes a microdelivery device which may be **implanted** in or otherwise administered to an **animal** or human. A microdelivery device is configured to have a plurality of compartments, each containing at least one drug so that a plurality of doses of the drug(s) are held within the device. In accordance with the present invention, the microdelivery device selectively actuates the compartments to selectively release doses of the drug(s) to provide an efficacious dosing pattern. One primary function of the present invention is to release two or more pesticides in such a pattern that parasites are effectively controlled while preventing the development of tolerance to the drugs within the parasites. Preferably, the microdelivery device is programmable to effectuate the release of the drug(s) at a desired time to maintain efficacious levels of the drug while minimizing the amount of drug which must be used.

AB The method for automatic dosing of drugs utilizes a microdelivery device which may be **implanted** in or otherwise administered to an **animal** or human. A microdelivery device is configured to have a plurality of compartments, each containing at least one drug so that a plurality of doses of the drug(s) are held within the device. In accordance with the present invention, the microdelivery device selectively actuates the compartments to selectively release doses of the drug(s) to provide an efficacious dosing pattern. One primary function of the present invention is to release two or more pesticides in such a pattern that parasites are effectively controlled while preventing the development of tolerance to the drugs within the parasites. Preferably, the microdelivery device is programmable to effectuate the release of the drug(s) at a desired time to maintain efficacious levels of the drug while minimizing the amount of drug which must be used.

SUMM Unfortunately, rounding up the animals each month, etc., is time consuming and expensive. The animal must be located and then brought to a suitable location for administration of the drug. Because of the time and expense involved with such round-ups, the farmer is forced into a compromise of overdosing the animal with a very large dose of the drug to prolong the period during which the drug is present at levels which meet or exceed the minimum effective level, thereby decrease the frequency with which the drugs must be administered, or accepting the expense of frequent round-ups to repetitively doses the animals. For example, a topically applied drug may have an efficacy threshold which relates to a 750 milligram dose of a given medication. However, to extend the period between dosing, a significantly larger dose is typically used. In FIG. 1, there is shown a curve indicating a normal, exponentially declining (i.e., first-order) efficacy curve where the drug is provided by prior art diffusion devices, such as **ear** tags, at a very high initial dose in order to maintain drug levels above the efficacy threshold for a prolonged period.

SUMM There have been numerous attempts to overcome these concerns. For

example, it has been proposed to **implant** in farm animals devices which provide for the release of drugs at a time other than **implantation**. Examples of such devices are included in the U.S. Pat. Nos. 4,564,363, 4,326,522, 4,425,117, 4,439,197, 3,840,009, 4,312,347 and 4,457,752. Unfortunately, these devices tend to be expensive to use, typically they allow only for a one time (continuous) discharge of a single drug, and are otherwise disadvantageous. Thus, there is a need for a method of administering drugs which overcomes the disadvantages of the prior art.

SUMM Additional objects of the invention include the use of devices which may be used topically, ruminally or **implanted**, and which may be used in both human and animal applications.

SUMM The above and other objects not specifically enumerated are realized in specific illustrated embodiments of a method for automatic repetitive dosing of a single drug or alternate dosing of two or more drugs including a microdelivery system which has at least two containers for holding at least a first drug and a second drug to be dosed and which is attached to, **implanted** in, or orally administered to the animal. The microdelivery system is programmed to release an initial dose of the first drug to the animal. The initial dose is then followed by periodic doses of the first or second drugs to achieve an efficacious treatment of the animal.

SUMM The microdelivery system is sufficiently small that it may be administered either topically, ruminally, or it may be **implanted** . If necessary, the dosages provided by the microdelivery system may be maintained within a single compartment for each dose, or larger doses may be achieved by using two or more compartments.

DETD Still another advantage of the method of the present invention is that the user can control when the microdelivery system 100 begins to administer the initial dose. A transmitter 170 can be provided to remotely transmit signals to the receiver and antenna 136. Signals from the transmitter 170 activate the timing circuit 132, thereby allowing the timing circuit to cause the drugs to be administered in a manner desired by the user. Thus, for example, a rancher could administer two microdelivery systems to each of his cattle, each of the microdelivery systems containing a six-month supply of antibiotics. One of the microdelivery systems would be activated to begin release of the antibiotics shortly after **implantation**. The other microdelivery system 100 could be activated approximately six months later by the transmitter 170. Thus, the rancher could reap the benefits of a one-year dosing regimen of antibiotics from a single administration of the dosage form. Annual administration of medication would save large amounts of time and money, by reducing animal handling and increasing the efficacy of the drugs. This method also provides a prolonged treatment period that can markedly exceed the duration of traditional diffusion devices, while eliminating concerns of host toxicity, subtherapeutic drug levels, development of parasite resistance, and tachyphylaxis.

DETD The microdelivery system 200 is advantageous in that the large number of vesicles 208 and 212 can hold numerous doses of the medications to be administered. For example, if alternating dosages are desired on a monthly basis, the microdelivery system 200 could provide drugs for more than a year without the need for **implanting** or otherwise administering additional dosage forms.

DETD Referring now to FIG. 4, there is shown a graph demonstrating a method of dosing in accordance with the principles of the present invention, along with a first-order kinetic decline after delivery of each dose. For illustration purposes, the amount of drug available on an **ear** tag device configuration that is available to kill flies is graphed.

DETD An initial dose 300 of a first drug, represented by solid line 304, is provided to kill flies. While referred herein as an **ear** tag which is clamped to an animal's **ear**, those skilled in the art will appreciate that the devices could be **implanted**, placed in the stomach of the animal, or placed in other areas. Additionally, the reference to a first drug should not be viewed as to limit the contents of a compartment of the microdelivery device, as two or more drugs could be disposed in a compartment of the microdelivery device for simultaneous administration.

DETD FIG. 4A shows a flow chart of the process used for implementing the dosing method demonstrated by the graph of FIG. 4. The initial step 320 is accomplished by administering the device to the animal. The device may be attached to a collar, **ear** tag or similar device to provide topical treatments, or may be conveniently **implanted**, such as in an animal's **ear** or orally administered for retention in the rumen of ruminant animals, to provide the drugs into the blood stream.

DETD In accordance with the graph and flow chart of FIGS. 4 and 4A, permethrin and chlorpyrifos insecticides are disposed in the microdelivery system 100 of FIGS. 2 and 2A and attached as an **ear** tag onto the **ear** of an animal for control of ectoparasites such as horn flies. The insecticides are formulated in combination with solvents, polymers and other additives as necessary to retard depletion of an expelled dose over a one-month period. A first dose of permethrin is supplied in sufficient quantity to raise the amount of available permethrin above the efficacy threshold. Applying a first-order kinetic depletion curve to the amount of permethrin that is available, the permethrin is formulated to stay above the efficacy threshold for one month. Similarly, the microdelivery system 100 is programmed to release a sufficient quantity of chlorpyrifos to bring the level of the drug above the efficacy threshold for chlorpyrifos and maintain a level above the efficacy threshold for one month. The microdelivery system 100 actuates a compartment holding the largest dose of chlorpyrifos four weeks after the first dose of permethrin is released.

DETD Referring now to FIG. 5, there is shown a graph of another dosing procedure in accordance with the present invention. An initial first dose 400 is provided of a first drug, the level of which is indicated by line 404. The initial first dose 400 of the first drug is approximately

1400 milligrams. At such a quantity, the amount of the first drug on the animal or available on a device configuration such as an **ear** tag, remains above the efficacy level 408 for approximately 60 days.

DETD While discussed primarily with respect to the control of parasites in animals, those skilled in the art will appreciate that the present method has a variety of medical applications. Thus, for example, a microdelivery device 100 or 200 could be programmed to provide medications in patterns which maximize their efficacy while minimizing adverse reactions or other problems. Furthermore, because the microdelivery devices are **implantable** or attachable to the patient, the drugs may be delivered in the most efficacious cycling while allowing the patient relative mobility. Thus, the principles of the present invention are equally applicable to medical applications in humans as it is to parasite control in animals.

CLM What is claimed is:

1. A method for automatic delivery of one or more drugs, the method comprising: a) selecting a microdelivery system having a plurality of compartments disposed therein for holding a plurality of doses of at least a first drug to be administered to an **animal**/human; b) administering the microdelivery system to the **animal**/human; c) actuating the microdelivery system to provide an initial dose of the first drug from at least one compartment of the microdelivery system to the **animal**/human in sufficient quantity to exceed the efficacy threshold for the first drug in the **animal**/human; and d) actuating the microdelivery system to provide a second dose of the first drug from at least one compartment of the microdelivery system to the **animal**/human at a predetermined time after the initial dose of the first drug and while the drug supplied by the initial dose remains above the efficacy threshold.

7. The method of claim 1 wherein step (b) comprises, more specifically, attaching the microdelivery system to the **animal**/human such that step (c) provides a topical application.

8. The method of claim 1, wherein step (b) comprises, more specifically, disposing the microdelivery system into the rumen of a ruminant **animal**.

9. The method of claim 1, wherein step (b) comprises, more specifically, **implanting** the microdelivery system into the **animal**/human.

11. The method according to claim 1, wherein the first drug is selected from the group consisting of permethrin, chlorpyrifos, diazinon, lambdacyhalothrin, pyrimiphos methyl, ivermectin, **doramectin**, moxidectin and insect growth regulators.

13. A method for automatic alternate dosing of at least two drugs in an **animal**, the method comprising: a) selecting a microdelivery system having a plurality of compartments disposed therein for holding at least a first drug and a second drug; b) administering the microdelivery system to the **animal**; c) actuating the microdelivery system to provide an initial dose of the first drug from a

compartment of the microdelivery system to the **animal**; and d) actuating the microdelivery system to provide an initial dose of the second drug from a compartment of the microdelivery system to the **animal** at a predetermined time after the initial dose of the first drug.

23. The method of claim 22, wherein the method further comprises releasing the compartments having the second quantity of the first drug at intervals sufficiently distant from one another so that the amount of the first drug available to the **animal** is substantially the same immediately after each dose of the first drug as the first quantity.

28. The method of claim 13, wherein step (a) comprises, more specifically, providing different quantities of the first and second drugs in the compartments, and wherein the method further comprises, selectively releasing the compartments to obtain a desired level of the first and second drugs within the **animal**.

29. The method of claim 13, wherein the method further comprises controlling the quantity of the first and second drugs within the **animal** by selectively controlling when each compartment releases the drug contained therein.

30. The method of claim 13, wherein steps (c) and (d) result in available levels of the first and second drugs to the **animal**, and wherein the method further comprises, delivering additional doses of the first and second drugs in such a manner to increase the levels of the drugs during seasonal parasite infestations.

31. The method of claim 13, wherein step (b) comprises, more specifically, **implanting** the microdelivery system within the **animal**.

32. The method of claim 13, wherein step (b) comprises, more specifically, topically attaching the microdelivery system to the **animal**.

33. The method of claim 13, wherein step (b) comprises, more specifically, disposing the microdelivery system within the stomach of the **animal**.

34. The method of claim 13, wherein the first drug is selected from the group consisting essentially of permethrin, chlorpyrifos, diazinon, permethrin, chlorpyrifos, diazinon, lambdacyhalothrin, pyrimiphos methyl, ivermectin, **doramectin**, and moxidectin.

35. The method of claim 34, wherein the second drug is selected from the group consisting essentially of permethrin, chlorpyrifos, diazinon, lambdacyhalothrin, pyrimiphos methyl, ivermectin, **doramectin**, and moxidectin.

36. A method for automatic alternate dosing of at least two drugs in an **animal**/human, each of the drugs having an efficacy threshold

level for the **animal**/human, the method comprising: a) selecting a microdelivery system having at least two compartments for holding at least first and second drugs; b) administering the microdelivery system to the **animal**/human; c) releasing a first dose of the first drug from the microdelivery system in sufficient quantity to exceed the efficacy threshold for the first drug for the **animal**/human; and d) releasing a first dose of the second drug from the microdelivery system in sufficient quantity to exceed the efficacy threshold of the second drug for the **animal**/human, while the level of the first drug remains above the efficacy threshold for the first drug.

37. The method for alternate dosing of at least two drugs of claim 36, wherein the method further comprises: e) releasing a second dose of the first drug from the microdelivery system in sufficient quantity so that the total quantity of the first drug administered to the **animal**/human exceeds the efficacy threshold for the first drug while the level of the second drug remains above the efficacy threshold for the second drug.

38. The method for alternate dosing of at least two drugs of claim 37, wherein the method further comprises: f) releasing a second dose of the second drug from the microdelivery system in sufficient quantity so that the total quantity of the second drug administered to the **animal**/human exceeds the efficacy threshold for the second drug while the level of the first drug remains above the efficacy threshold for the first drug.

39. The method for alternate dosing of at least two drugs of claim 38, wherein the second dose of the first drug is released while the level of the first drug administered to the **animal**/human remains above the efficacy threshold for the first drug.

42. The method for alternate dosing of at least two drugs of claim 41, further comprising programming the microdelivery system to release an initial dose of the first drug in sufficient quantity that the first drug provided to the **animal**/human will remain at a level exceeding the efficacy threshold for the first drug until the second drug is released.

45. The method for alternate dosing of at least two drugs of claim 36, wherein step (b) comprises attaching the microdelivery system to the **animal**/human so as to provide topical delivery when a dose is released.

46. The method for alternate dosing of at least two drugs of claim 36, wherein step (b) comprises disposing the microdelivery system in the rumen of an **animal**.

47. The method for alternate dosing of at least two drugs of claim 36, wherein step (b) comprises **implanting** the microdelivery system to the **animal**/human so as to provide internal delivery when a dose is released.

50. The method of claim 36, wherein the first drug is selected from the group consisting essentially of permethrin, chlorpyrifos, diazinon, lambdacyhalothrin, pyrimiphos methyl, ivermectin, **doramectin**, and moxidectin.

51. The method of claim 50, wherein the second drug is selected from the group consisting essentially of permethrin, chlorpyrifos, diazinon, lambdacyhalothrin, pyrimiphos methyl, ivermectin, **doramectin**, and moxidectin.

L60 ANSWER 4 OF 8 USPATFULL
AN 1998:28099 USPATFULL
TI Systemic control of parasites
IN Miller, Thomas A., Carrollton, TX, United States
PA Virbac, Inc., Ft. Worth, TX, United States (U.S. corporation)
PI US 5728719 19980317
AI US 1995-403414 19950314 (8)
RLI Division of Ser. No. US 1994-210135, filed on 17 Mar 1994, now patented, Pat. No. US 5439924 which is a continuation of Ser. No. US 1992-980591, filed on 23 Nov 1992, now abandoned which is a continuation-in-part of Ser. No. US 1991-812430, filed on 23 Dec 1991, now abandoned
DT Utility
FS Granted
EXNAM Primary Examiner: Dean, Karen A.
LREP McGregor, Martin L.
CLMN Number of Claims: 35
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1623
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention is a method for controlling ectoparasites. More particularly, the invention relates to a method of treatment in which the warm blooded **animal** is dosed with an ovicidally effective amount of a heterocyclic nitrogen compound selected from the group represented by the formula: ##STR1## wherein R.sub.1, is either one of the following groups: ##STR2## in which R.sub.7, R.sub.8, R.sub.9, R.sub.10, R.sub.11, R.sub.12, R.sub.13, R.sub.14, R.sub.15, R.sub.16, and R.sub.17 are, the same or different, each a hydrogen atom, a halogen atom, a C.sub.1 -C.sub.4 alkoxy group, a C.sub.1 -C.sub.4 alkylthio group, a trifluoro methyl group or a vitro group, R.sub.18, R.sub.19, R.sub.20 and R.sub.21 are, the same or different, each a hydrogen atom or a methyl group, k is an integer of 0 to 1 and 1 is an integer of 0 to 3; R.sub.2 and R.sub.3 are, the same or different, each a hydrogen atom, a halogen atom or a methyl group; R.sub.4 is a halogen atom or a methyl group; R.sub.5 and R.sub.6 are, the same or different, each a hydrogen atom, a halogen atom, a C.sub.1 -C.sub.4 haloalkyl group or a C.sub.1 -C.sub.4 haloalkoxy group; X, Y and Z are, the same or different, each an oxygen atom, a sulfur atom or a methylene group, m is an integer of 0 to 4, and n is an integer of 0 to 2, which is transmitted to the ectoparasite by the **animal**'s blood. In a further embodiment, a

compound selected from the group consisting of ivermectin, **milbemycin**, **milbemycin** oxime, moxidectin and **avermectin** and **avermectin** derivatives.

AB The present invention is a method for controlling ectoparasites. More particularly, the invention relates to a method of treatment in which the warm blooded **animal** is dosed with an ovicidally effective amount of a heterocyclic nitrogen compound selected from the group represented by the formula: ##STR1## wherein R.sub.1, is either one of the following groups: ##STR2## in which R.sub.7, R.sub.8, R.sub.9, R.sub.10, R.sub.11, R.sub.12, R.sub.13, R.sub.14, R.sub.15, R.sub.16, and R.sub.17 are, the same or different, each a hydrogen atom, a halogen atom, a C.sub.1 -C.sub.4 alkoxy group, a C.sub.1 -C.sub.4 alkylthio group, a trifluoro methyl group or a vitro group, R.sub.18, R.sub.19, R.sub.20 and R.sub.21 are, the same or different, each a hydrogen atom or a methyl group, k is an integer of 0 to 1 and 1 is an integer of 0 to 3; R.sub.2 and R.sub.3 are, the same or different, each a hydrogen atom, a halogen atom or a methyl group; R.sub.4 is a halogen atom or a methyl group; R.sub.5 and R.sub.6 are, the same or different, each a hydrogen atom, a halogen atom, a C.sub.1 -C.sub.4 haloalkyl group or a C.sub.1 -C.sub.4 haloalkoxy group; X, Y and Z are, the same or different, each an oxygen atom, a sulfur atom or a methylene group, m is an integer of 0 to 4, and n is an integer of 0 to 2, which is transmitted to the ectoparasite by the **animal**'s blood. In a further embodiment, a compound selected from the group consisting of ivermectin, **milbemycin**, **milbemycin** oxime, moxidectin and **avermectin** and **avermectin** derivatives.

SUMM Heartworm, ascarid and hookworm infections of dogs and cats can be prevented by administration of the antibiotic avermectin compounds by parenteral injection, oral dosage, transdermal application and by **implanting** solid or hollow devices designed to provide extended controlled release of the active compound. For instance, milbemycin, ivermectin, milbemycin oxime and moxidectin can be administered monthly to prevent and cure heartworm, hookworms and ascarids of dogs and cats.

SUMM A particularly convenient method of preventing infection and disease caused by these endoparasites, and in controlling ectoparasitic infestation, is the combination in a single product of a systemically active nitrogen containing heterocyclic compound of the invention as defined above and one of the compounds of the antibiotic class effective against endoparasites (e.g., including but not limited to milbemycin, ivermectin, milbemycin oxime and moxidectin). Administration of this convenient, effective and safe combination can be made by daily or periodic treatment (e.g., monthly) with liquid, chewable wafer or tablet oral dose forms, by parenteral injection, or by less frequent **implantation** of a controlled release device that contains and releases both a systemically active juvenile hormone-like nitrogen containing heterocyclic compound and a systemically active antibiotic effective against nematode parasites at rates that achieve and maintain blood levels adequate to affect the target endo- and ectoparasites.

SUMM It is an essential feature of the present invention that the active

compound is administered in such a manner that it can be ingested by the feeding parasite along with the blood of the host animal, and can then exhibit activity against the egg. As used herein, "host" means a host animal whose blood will permit an ectoparasite to achieve normal reproductive capabilities. As used herein, "ovicidally effective" means an effect which leads to a reduced rate of hatching of eggs or to the inability of the male to fertilize eggs, resulting in sterile egg production. In accordance with the present invention, this is achieved by several forms of application, for example, by administering a formulated active ingredient orally, parenterally, by **implant**, or as a bolus. In this case, the term "formulated" means in the form of a powder, a tablet, a wafer, a granulet, a capsule, an emulsion, a gel, a foam, or other compositions suitable for administering an effective amount of the active ingredient. The preparation does not necessarily have to be administered to the animal directly; it may be convenient to mix it with the animal's feed. In addition to containing adjuvants conventionally employed in the art of formulation, the compositions to be administered orally may of course contain further additives which stimulate voluntary ingestion by the animal, such as suitable scents or flavorings. Owing to its simplicity, oral application is one of the preferred modes of the present invention. A further mode of application is parenteral, for example, by subcutaneous, intravenous, or intramuscular injection, or by means of a sustained action preparation in the form of an **implant**, bolus, or other sustained release formulation. The application may be in a multiple dose or a single dose form.

SUMM Methods of oral application include, but are not limited to, compounds premixed in animal food, fed in biscuits or treats, chewable tablets or wafers, water dissolvable capsules or tablets, emulsifiable concentrates, water soluble compounds applied with a dropper into water, or materials applied in any form onto pet food. **Implants** may include any device applied to the animal for release of compounds to control ectoparasites. It is contemplated that the present invention may also be delivered to the animal by a transdermal transport system. Percutaneous administration is conveniently accomplished by subcutaneous, dermal, intramuscular, and even intravenous application of the injectable formulation. Conventional needle-type injection devices, as well as needleless air blast injection devices, as well as pour-on and spot-on formulations may be useful. It is possible to delay or sustain the permeation of the active ingredient through the animal's living tissues by proper formulation.

SUMM Sustained action of the active ingredient can be obtained by formulating the compound in a matrix that will physically inhibit dissolution. The formulated matrix is injected or otherwise surgically **implanted** into the body, where it remains as a depot from which the compound slowly dissolves, or in the case of hydrophobic compounds, is released by diffusion. Matrix formulations now known in the an are formulated in waxy semi-solids such as vegetable waxes and high molecular weight polyethylene glycols. Very effective sustained action is obtained by introducing into the animal an **implant** containing the active

ingredient. Such **implants** are now well known in the veterinary art and are usually made of a silicon rubber or other polymerized plastic such as methacrylate. An especially useful **implant** composition is disclosed in U.S. Pat. No. 4,696,974. The active ingredient is dispersed through the solid **implant** or is contained inside a hollow **implant**. The active ingredient is dispersed by first dissolving or mixing with the polymer, or dissolved in, or mixed with a carrier, it is dispersed within the polymer. After **implantation**, the active ingredient diffuses or leaches out of the solid or hollow **implant** into the body fluids of the treated animal.

SUMM The rate at which the active ingredient is released from an **implant**, and hence, the length of time during which the **implant** remains effective, is controlled with good accuracy by the proper adjustment of the concentration of the compound in the **implant**, the external area of and amount of carrier in the **implant**, the external area of the **implant**, the formulation of the polymer from which the **implant** is made, the thickness of the wall of hollow **implants** and the diffusion characteristics of the active or carrier/active solution through the wall of the **implant** or through specially designed end-plugs of polymer or other membrane forming one or more surfaces of the **implant**, or by being forced through a porous membrane or aperture by an osmotic pump activated by absorption of body water into an osmotically active component contained in a second compartment of a hollow **implant**.

SUMM Administration of the active ingredient by means of an **implant** is a further particularly preferred embodiment. Such administration is highly economical and efficacious because a properly designed **implant** maintains a constant concentration of the compound in the tissues of the host animal, can be designed to supply a compound for several months, and is easily inserted in the animal. No further handling of the animal or concern over the dosage is necessary after **implant** insertion. Said **implant** may be erodible/soluble and may be left in the animal tissue, or it may be insoluble/non-erodible and suitable for surgical removal after exhaustion of its active ingredient.

SUMM The present invention is also directed to a method of systemically preventing the infestation of dogs and cats by fleas, which method comprises administering to said host animals orally, parenterally, or by **implant** an ovicidally effective amount of a compound of the formula: ##STR5## wherein R.sub.1, is either one of the following groups: ##STR6## (in which R.sub.7, R.sub.8, R.sub.9, R.sub.10, R.sub.11, R.sub.12, R.sub.13, R.sub.14, R.sub.15, R.sub.16, and R.sub.17 are, the same or different, each a hydrogen atom, a halogen atom, a C.sub.1 -C.sub.4 alkoxy group, a C.sub.1 -C.sub.4 alkythio group, a trifluoro methyl group or a nitro group; R.sub.18, R.sub.19, R.sub.20 and R.sub.21 are, the same or different, each a hydrogen atom or a methyl group, k is an integer of 0 to 1 and l is an integer of 0 to 3;) R.sub.2 and R.sub.3 are, the same or different, each a hydrogen atom, a halogen atom or a methyl group; R.sub.4 is a halogen atom or a methyl

group; R.sub.5 and R.sub.6 are, the same or different, each a hydrogen atom, a halogen atom, a C.sub.1 -C.sub.4 haloalkyl group or a C.sub.1 -C.sub.4 haloalkoxy group; X, Y and Z are, the same or different, each an oxygen atom, a sulfur atom or a methylene group, m is an integer of 0 to 4, and n is an integer of 0 to 2, which is transmitted to the ectoparasite by the animal's blood.

SUMM Commercial products may be formulated as concentrates, from which the end user will normally employ dilute formulations. The compositions may also contain further ingredients such as stabilizers, antioxidants, anti-foams, viscosity regulators, binders, tactifiers, preservatives, as well as other known and active ingredients for obtaining special effects. Materials known from veterinary practice as being suitable for being oral parenteral or **implant** administration may be employed as formulation assists. A number of examples are cited below.

DETD Monolithic 150 mg **Implant**

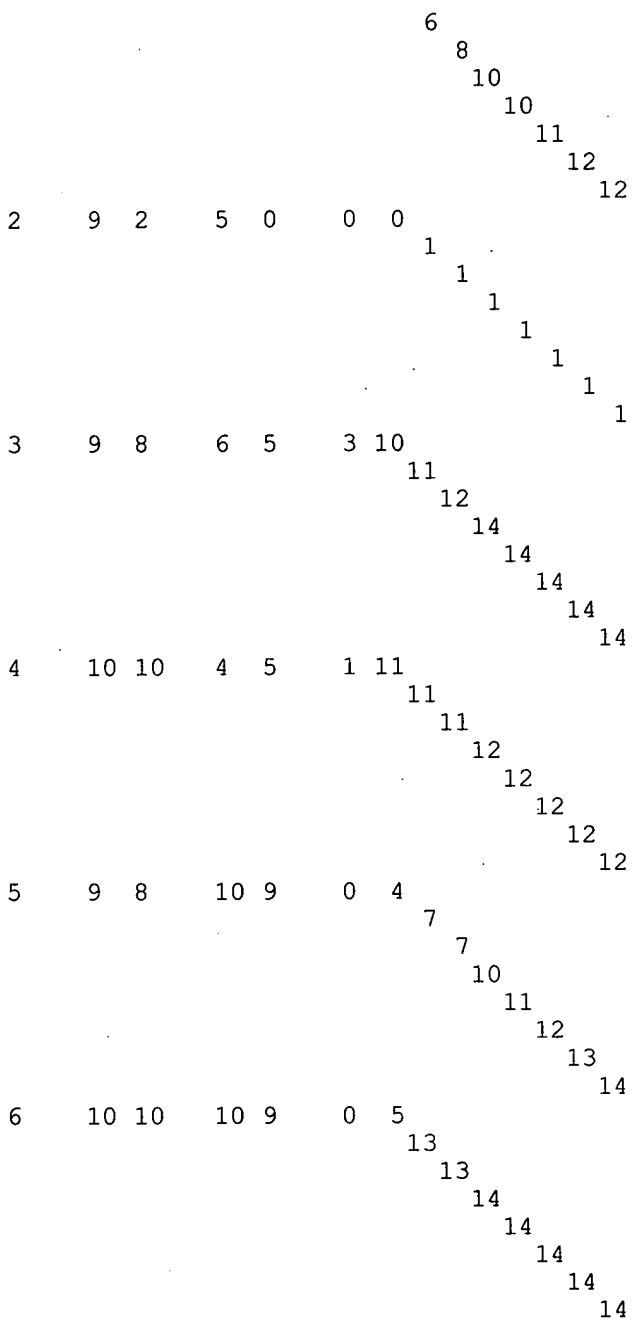
DETD The active ingredient, for example pyriproxifen, is mixed with the prepared hydrophilic copolymer powder to which is added the silicone composite, for instance hydroxy-hydrogen-poly (dimethylsiloxane) and methyltriacetoxysiloxane cross linking agent in the proportions shown. The mixture is reacted at ambient temperature in a mold for 12 hours. **Implants** are sterilized by gamma radiation or by gassing with ethylene oxide after packaging. **Implants** are inserted subcutaneously either by trochar or by minor surgical procedure. Multiple **implants** may be inserted simultaneously depending on the animal's weight, on the known release rate of active ingredient and on the desired frequency of replantation. The example single **implant** provides adequate blood levels for 90 days to sterilize all eggs laid by female fleas feeding on an **implanted** cat weighing 3 kg.

DETD Ten (10) ticks (Dermacentor variabilis) were applied to each **ear** of each rabbit and enclosed in cotton **ear** bags to restrain the ticks and enable their recovery after engorgement. After application of the ticks, the **ear** bags were examined daily and the times at which male and female ticks became engorged and detached were recorded (Table 6).

DETD TABLE 6

PYRIPROXIFEN INSECT GROWTH REGULATOR ORAL EFFECT ON FERTILITY OF TICK EGGS.

Tick attachment/Engorgement											
No. ticks attached			Cumulative engorged/detached								
Rabbit											
	Left **Ear**										
		Right **Ear**									
			Days after attachment								
No.	Male										
	Female										
		Male									
			Female								
				3	4	5	6	7	8	9	10
											11



DETD Monolithic 300 mg **implant**

DETD The active ingredient is mixed with the prepared hydrophilic copolymer powder to which is added the silicone composite, for instance hydroxy-hydrogen-poly (dimethylsiloxane) and methyltriacetoxysiloxane cross linking agent in the proportions shown. The mixture is reacted at ambient temperature in a mold for 12 hours. **Implants** are sterilized by gamma radiation or by gassing with ethylene oxide after packaging. **Implants** are inserted subcutaneously either by

trochar or by minor surgical procedure. Multiple **implants** may be inserted simultaneously depending on the animal's weight, on the known release rate of active ingredient, and on the desired frequency of reimplantation. The example single **implant** provides adequate blood levels for 90 days to sterilize all eggs laid by female fleas and preventing heartworm transmission by all mosquitoes feeding on an **implanted** dog weighing 6 kg. Multiple or larger **implants** may be administered to larger dogs, and **implants** may easily be removed after pay-out. By altering the physical characteristics of **implants**, longer pay-out and/or different release rates may be obtained.

CLM What is claimed is:

1. A composition comprising a pharmaceutically acceptable carrier for veterinary use, the composition being formulated to deliver an amount in the range of 0.001 mg to 1000 mg of compound per kilogram of **animal** body weight to produce when administered to a host **animal** an ovicidally effective amount of a compound having the formula: ##STR7## in which R.sub.7, R.sub.8, R.sub.9, R.sub.10, R.sub.11, R.sub.12, R.sub.13, R.sub.14, R.sub.15, R.sub.16, and R.sub.17, are, the same or different, each a hydrogen atom, a halogen atom, a C.sub.1 -C.sub.4 alkoxy group, a C.sub.1 -C.sub.4 alkylthio group, trifluoro methyl group, or a nitro group; R.sub.18, R.sub.19, R.sub.20 and R.sub.21 are, the same or different, each a hydrogen atom, or a methyl group, k is an integer of 0 to 3; R.sub.2 and R.sub.3 are, the same or different, each a hydrogen atom, or a methyl group; R.sub.4 is a halogen atom, or a methyl group, R.sub.5 and R.sub.6 are, the same or different, each a hydrogen atom, a halogen atom, a C.sub.1 -C.sub.4 alkoxy group, or a C.sub.1 -C.sub.4 haloalkyloxy group; X, Y and Z are, the same or different, each an oxygen atom, a sulfur atom or a methylene group, m is an integer of 0 to 4 and n is an integer of 0 to 2, in blood of the host **animal**.

9. A dietary supplement composition comprising a pharmaceutically acceptable carrier for veterinary use formulated to deliver an amount in the range of 0.001 mg to 1000 mg of compound per kilogram of **animal** body weight to produce when administered to a host **animal** in the host **animal**'s blood an ovicidally effective amount of a compound having the formula: ##STR8## wherein R.sub.1 is selected from the group consisting of ##STR9## in which R.sub.7, R.sub.8, R.sub.9, R.sub.10, R.sub.11, R.sub.12, R.sub.13, R.sub.14, R.sub.15, R.sub.16, and R.sub.17, are, the same or different, each a hydrogen atom, a halogen atom, a C.sub.1 -C.sub.4 alkoxy group, a C.sub.1 -C.sub.4 alkylthio group, trifluoro methyl group, or a nitro group; R.sub.18, R.sub.19, R.sub.20 and R.sub.21 are, the same or different, each a hydrogen atom, or a methyl group, k is an integer of 0 to 3; R.sub.2 and R.sub.3 are, the same or different, each a hydrogen atom, or a methyl group; R.sub.4 is a halogen atom, or a methyl group, R.sub.5 and R.sub.6 are, the same or different, each a hydrogen atom, a halogen atom, a C.sub.1 -C.sub.4 alkoxy group, or a C.sub.1 -C.sub.4 haloalkyloxy group; X, Y and Z are, the same or different, each an

oxygen atom, a sulfur atom or a methylene group, m is an integer of 0 to 4 and n is an integer of 0 to 2, which is transmitted to an ectoparasite feeding on the **animal**'s blood.

10. A dietary supplement according to claim 9 wherein the compounds selected are pyriproxifen in the range of about 0.01 mg/kg to about 200 mg/kg and **milbemycin** in the range of about 0.5 mcg/kg to about 100 mg/kg.

12. A dietary supplement according to claim 9 wherein the compounds selected are pyriproxifen in the range of about 0.01 mg/kg to about 200 mg/kg and **milbemycin** oxime in the range of about 0.5 mcg/kg to about 100 mg/kg.

14. The composition of claim 1 wherein the composition is formulated to deliver a dosage of from 0.01 mg to 100 mg per kilogram of **animal** body weight to the **animal**.

15. The composition of claim 1 wherein the composition is formulated to deliver a dosage of from 0.01 mg to 70 mg per kilogram of **animal** body weight to the **animal**.

16. The composition of claim 1 wherein the composition is formulated to deliver a dosage of from 0.02 mg to 50 mg per kilogram of **animal** body weight to the **animal**.

17. The composition of claim 1 wherein the composition is formulated to deliver the dosage to the **animal** by a transdermal transmission.

19. The composition of claim 1 wherein the composition is formulated to deliver a sustained release dosage to the **animal**.

20. The dietary supplement composition of claim 9 wherein the composition is formulated to deliver a dosage of from 0.01 mg to 100 mg per kilogram of **animal** body weight to the **animal**.

21. The dietary supplement composition of claim 9 wherein the composition is formulated to deliver a dosage of from 0.01 mg to 70 mg per kilogram of **animal** body weight to the **animal**.

22. The dietary supplement composition of claim 9 wherein the composition is formulated to deliver a dosage of from 0.02 mg to 50 mg per kilogram of **animal** body weight to the **animal**.

24. A composition comprising pyriproxifen formulated to deliver a sufficient amount of pyriproxifen to the blood of a host **animal** to provide an ovicidally effective concentration to an ectoparasite feeding on the blood of the **animal**.

25. A composition formulated as a single dose in the range of about 10 to 200 mg/kg of 2-[1-methyl-2-(4-phenoxyphenoxy)ethoxy]pyridine (pyriproxifen) with a pharmaceutically acceptable carrier chosen to deliver an ovicidally effective amount to the **animal**'s blood stream for at least 25 days.

26. A composition according to claim 25 which further comprises 0.5 mcg/kg to 100 mg/kg of a parasite control compound selected from the group consisting of **avermectin**, **avermectin** derivatives, **milbemycin**, **milbemycin** derivatives, ivermectin, ivermectin derivatives, **milbemycin** oxime, **milbemycin** oxime derivatives, moxidectin, and moxidectin derivatives, or mixtures thereof.

27. A composition according to claim 25 formulated as an **implant** .

28. A composition according to claim 26 formulated as an **implant** .

29. A composition according to claim 24 which comprises a dose in the range of 0.001 to 1000 mg/kg of host **animal** body weight.

34. A composition according to claim 1 which comprises a parasiticidally effective amount of a compound selected from the group consisting of **avermectin**, **avermectin** derivatives, **milbemycin** , **milbemycin** derivatives, ivermectin, ivermectin derivatives, **milbemycin** oxime, **milbemycin** oxime derivatives, moxidectin, and moxidectin derivatives, or mixtures thereof.

35. A composition according to claim 9 which comprises a parasiticidally effective amount of a compound selected from the group consisting of **avermectin**, **avermectin** derivatives, **milbemycin** , **milbemycin** derivatives, ivermectin, ivermectin derivatives, **milbemycin** oxime, **milbemycin** oxime derivatives, moxidectin, and moxidectin derivatives, or mixtures thereof.

IT **51570-36-6**, Milbemycin **51570-36-6D**, Milbemycin, derivs.
70288-86-7, Ivermectin 70288-86-7D, Ivermectin, derivs.
73989-17-0, Avermectin **73989-17-0D**, Avermectin, derivs.
113507-06-5, Moxidectin 113507-06-5D, Moxidectin, derivs.
129496-10-2, Milbemycin oxime 129496-10-2D, Milbemycin oxime, derivs.
(systemic ectoparasiticides contg. heterocyclic compd. and)

L60 ANSWER 5 OF 8 USPATFULL
AN 95:71374 USPATFULL
TI Systemic control of parasites
IN Miller, Thomas A., Carrollton, TX, United States
PA Virbac, Inc., Fort Worth, TX, United States (U.S. corporation)
PI US 5439924 19950808
AI US 1994-210135 19940317 (8)
RLI Continuation of Ser. No. US 1992-980591, filed on 23 Nov 1992, now abandoned which is a continuation-in-part of Ser. No. US 1991-812430, filed on 23 Dec 1991, now abandoned
DT Utility
FS Granted
EXNAM Primary Examiner: Richter, Johann; Assistant Examiner: Hydorn, Michael B.
LREP Baker & Botts
CLMN Number of Claims: 37

ECL Exemplary Claim: 25
DRWN No Drawings
LN.CNT 1616
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention is a method for controlling ectoparasites. More particularly, the invention relates to a method of treatment in which the warm blooded **animal** is dosed with an ovicidally effective amount of a heterocyclic nitrogen compound selected from the group represented by the formula: ##STR1## wherein R.sub.1, is either one of the following groups: ##STR2## R.sub.2 and R.sub.3 are the same or different, each a hydrogen atom, a halogen atom or a methyl group; R.sub.4 is a halogen atom or a methyl group; R.sub.5 and R.sub.6 are the same or different, each a hydrogen atom, a halogen atom, a C.sub.1 -C.sub.4 haloalkyl group or a C.sub.1 -C.sub.4 haloalkoxy group; X, Y and Z are the same or different, each an oxygen atom, a sulfur atom or a methylene group, which is transmitted to the ectoparasite by the **animal**'s blood. In a further embodiment, a compound selected from the group consisting of ivermectin, **milbemycin**, **milbemycin** oxime, moxidectin and **avermectin** and **avermectin** derivatives.
AB The present invention is a method for controlling ectoparasites. More particularly, the invention relates to a method of treatment in which the warm blooded **animal** is dosed with an ovicidally effective amount of a heterocyclic nitrogen compound selected from the group represented by the formula: ##STR1## wherein R.sub.1, is either one of the following groups: ##STR2## R.sub.2 and R.sub.3 are the same or different, each a hydrogen atom, a halogen atom or a methyl group; R.sub.4 is a halogen atom or a methyl group; R.sub.5 and R.sub.6 are the same or different, each a hydrogen atom, a halogen atom, a C.sub.1 -C.sub.4 haloalkyl group or a C.sub.1 -C.sub.4 haloalkoxy group; X, Y and Z are the same or different, each an oxygen atom, a sulfur atom or a methylene group, which is transmitted to the ectoparasite by the **animal**'s blood. In a further embodiment, a compound selected from the group consisting of ivermectin, **milbemycin**, **milbemycin** oxime, moxidectin and **avermectin** and **avermectin** derivatives.
SUMM Heartworm, ascarid and hookworm infections of dogs and cats can be prevented by administration of the antibiotic avermectin compounds by parenteral injection, oral dosage, transdermal application and by **implanting** solid or hollow devices designed to provide extended controlled release of the active compound. For instance, milbemycin, ivermectin, milbemycin oxime and moxidectin can be administered monthly to prevent and cure heartworm, hookworms and ascarids of dogs and cats.

SUMM A particularly convenient method of preventing infection and disease caused by these endoparasites, and in controlling ectoparasitic infestation, is the combination in a single product of a systemically active nitrogen containing heterocyclic compound of the invention as defined above and one of the compounds of the antibiotic class effective against endoparasites (e.g., including but not limited to milbemycin, ivermectin, milbemycin oxime and moxidectin). Administration of this convenient, effective and safe combination can be made by daily or

periodic treatment (e.g., monthly) with liquid, chewable wafer or tablet oral dose forms, by parenteral injection, or by less frequent **implantation** of a controlled release device that contains and releases both a systemically active juvenile hormone-like nitrogen containing heterocyclic compound and a systemically active antibiotic effective against nematode parasites at rates that achieve and maintain blood levels adequate to affect the target endo- and ectoparasites.

SUMM It is an essential feature of the present invention that the active compound is administered in such a manner that it can be ingested by the feeding parasite along with the blood of the host animal, and can then exhibit activity against the egg. As used herein, "host" means a host animal whose blood will permit an ectoparasite to achieve normal reproductive capabilities. As used herein, "ovicidally effective" means an effect which leads to a reduced rate of hatching of eggs or to the inability of the male to fertilize eggs, resulting in sterile egg production. In accordance with the present invention, this is achieved by several forms of application, for example, by administering a formulated active ingredient orally, parenterally, by **implant**, or as a bolus. In this case, the term "formulated" means in the form of a powder, a tablet, a wafer, a granulet, a capsule, an emulsion, a gel, a foam, or other compositions suitable for administering an effective amount of the active ingredient. The preparation does not necessarily have to be administered to the animal directly; it may be convenient to mix it with the animal's feed. In addition to containing adjuvants conventionally employed in the art of formulation, the compositions to be administered orally may of course contain further additives which stimulate voluntary ingestion by the animal, such as suitable scents or flavorings. Owing to its simplicity, oral application is one of the preferred modes of the present invention. A further mode of application is parenteral, for example, by subcutaneous, intravenous, or intramuscular injection, or by means of a sustained action preparation in the form of an **implant**, bolus, or other sustained release formulation. The application may be in a multiple dose or a single dose form.

SUMM Methods of oral application include, but are not limited to, compounds premixed in animal food, fed in biscuits or treats, chewable tablets or wafers, water dissolvable capsules or tablets, emulsifiable concentrates, water soluble compounds applied with a dropper into water, or materials applied in any form onto pet food. **Implants** may include any device applied to the animal for release of compounds to control ectoparasites. It is contemplated that the present invention may also be delivered to the animal by a transdermal transport system. Percutaneous administration is conveniently accomplished by subcutaneous, dermal, intramuscular, and even intravenous application of the injectable formulation. Conventional needle-type injection devices, as well as needleless air blast injection devices, as well as pour-on and spot-on formulations may be useful. It is possible to delay or sustain the permeation of the active ingredient through the animal's living tissues by proper formulation.

SUMM Sustained action of the active ingredient can be obtained by formulating the compound in a matrix that will physically inhibit dissolution. The formulated matrix is injected or otherwise surgically **implanted** into the body, where it remains as a depot from which the compound slowly dissolves, or in the case of hydrophobic compounds, is released by diffusion. Matrix formulations now known in the art are formulated in waxy semi-solids such as vegetable waxes and high molecular weight polyethylene glycols. Very effective sustained action is obtained by introducing into the animal an **implant** containing the active ingredient. Such **implants** are now well known in the veterinary art and are usually made of a silicon rubber or other polymerized plastic such as methacrylate. An especially useful **implant** composition is disclosed in U.S. Pat. No. 4,696,974. The active ingredient is dispersed through the solid **implant** or is contained inside a hollow **implant**. The active ingredient is dispersed by first dissolving or mixing with the polymer, or dissolved in, or mixed with a carrier, it is dispersed within the polymer. After **implantation**, the active ingredient diffuses or leaches out of the solid or hollow **implant** into the body fluids of the treated animal.

SUMM The rate at which the active ingredient is released from an **implant**, and hence, the length of time during which the **implant** remains effective, is controlled with good accuracy by the proper adjustment of the concentration of the compound in the **implant**, the external area of and amount of carrier in the **implant**, the external area of the **implant**, the formulation of the polymer from which the **implant** is made, the thickness of the wall of hollow **implants** and the diffusion characteristics of the active or carder/active solution through the wall of the **implant** or through specially designed end-plugs of polymer or other membrane forming one or more surfaces of the **implant**, or by being forced through a porous membrane or aperture by an osmotic pump activated by absorption of body water into an osmotically active component contained in a second compartment of a hollow **implant**.

SUMM Administration of the active ingredient by means of an **implant** is a further particularly preferred embodiment. Such administration is highly economical and efficacious because a properly designed **implant** maintains a constant concentration of the compound in the tissues of the host animal, can be designed to supply a compound for several months, and is easily inserted in the animal. No further handling of the animal or concern over the dosage is necessary after **implant** insertion. Said **implant** may be erodible/soluble and may be left in the animal tissue, or it may be insoluble/non-erodible and suitable for surgical removal after exhaustion of its active ingredient.

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implant an ovicidally effective amount of a compound of the formula: ##STR5## wherein R.sub.1, is either one of the following groups: ##STR6## (in which R.sub.7, R.sub.8, R.sub.9, R.sub.10, R.sub.11, R.sub.12, R.sub.13, R.sub.14, R.sub.15, R.sub.16, R.sub.17 are, the same or different, each a hydrogen atom, a halogen atom, a C.sub.1 -C.sub.4 alkoxy group, a C.sub.1 -C.sub.4 alkylthio group, a trifluoro methyl group or a nitro group; R.sub.18, R.sub.19, R.sub.20 and R.sub.21 are, the same or different, each a hydrogen atom or a methyl group, k is an integer of 0 to 1 and l is an integer of 0 to 3;) R.sub.2 and R.sub.3 are, the same or different, each a hydrogen atom, a halogen atom or a methyl group; R.sub.4 is a halogen atom or a methyl group; R.sub.5 and R.sub.6 are, the same or different, each a hydrogen atom, a halogen atom, a C.sub.1 -C.sub.4 haloalkyl group or a C.sub.1 -C.sub.4 haloalkoxy group; X, Y and Z are, the same or different, each an oxygen atom, a sulfur atom or a methylene group, m is an integer of 0 to 4, and n is an integer of 0 to 2, which is transmitted to the ectoparasite by the animal's blood.

SUMM Commercial products may be formulated as concentrates, from which the end user will normally employ dilute formulations. The compositions may also contain further ingredients such as stabilizers, antioxidants, anti-foams, viscosity regulators, binders, tactifiers, preservatives, as well as other known and active ingredients for obtaining special effects. Materials known from veterinary practice as being suitable for being oral parenteral or **implant** administration may be employed as formulation assists. A number of examples are cited below.

DETD Monolithic 150 mg **Implant**:

DETD The active ingredient, for example pyriproxifen, is mixed with the prepared hydrophilic copolymer powder to which is added the silicone composite, for instance hydroxy-hydrogen-poly(dimethylsiloxane) and methyltriacetoxysiloxane cross linking agent in the proportions shown. The mixture is reacted at ambient temperature in a mold for 12 hours. **Implants** are sterilized by gamma radiation or by gassing with ethylene oxide after packaging. **Implants** are inserted subcutaneously either by trochar or by minor surgical procedure. Multiple **implants** may be inserted simultaneously depending on the animal's weight, on the known release rate of active ingredient and on the desired frequency of reimplantation. The example single **implant** provides adequate blood levels for 90 days to sterilize all eggs laid by female fleas feeding on an **implanted** cat weighing 3 kg.

DETD Ten (10) ticks (Dermacentor variabilis) were applied to each **ear** of each rabbit and enclosed in cotton **ear** bags to restrain the ticks and enable their recovery after engorgement. After application of the ticks, the **ear** bags were examined daily and the times at which male and female ticks became engorged and detached were recorded (Table 6).

DETD TABLE 6

PYRIPROXIFEN INSECT GROWTH REGULATOR ORAL EFFECT ON FERTILITY OF TICK EGGS.

Tick attachment/Engorgement

No. ticks attached

Cumulative engorged/detached

Rabbit
Left **Ear**
Right **Ear**
Days after attachment

No.	Male	Female	Male	Female	3 4 5 6 7 8 9 10 11
1	9	9	7	1	0 5 6 8 10 10 11 12 12
2	9	2	5	0	0 0 1 1 1 1 1 1 1
3	9	8	6	5	3 10 11 12 14 14 14 14 14
4	10	10	4	5	1 11 11 11 12 12 12 12 12
5	9	8	10	9	0 4 7 7 10 11 12 13 14
6	10	10	10	9	0 5 13 13 14 14 14 14 14

DETD Monolithic 300 mg **implant**:
DETD The active ingredient is mixed with the prepared hydrophilic copolymer powder to which is added the silicone composite, for instance hydroxy-hydrogen-poly (dimethylsiloxane) and methyltriacetoxysiloxane cross linking agent in the proportions shown. The mixture is reacted at ambient temperature in a mold for 12 hours. **Implants** are sterilized by gamma radiation or by gassing with ethylene oxide after packaging. **Implants** are inserted subcutaneously either by trochar or by minor surgical procedure. Multiple **implants** may be inserted simultaneously depending on the animal's weight, on the

known release rate of active ingredient, and on the desired frequency of reimplantation. The example single **implant** provides adequate blood levels for 90 days to sterilize all eggs laid by female fleas and preventing heartworm transmission by all mosquitoes feeding on an **implanted** dog weighing 6 kg. Multiple or larger **implants** may be administered to larger dogs, and **implants** may easily be removed after pay-out. By altering the physical characteristics of **implants**, longer pay-out and/or different release rates may be obtained.

CLM What is claimed is:

1. A method for the systemic control of ectoparasites which attack warm blooded **animals**, comprising administering to a warm blooded **animal** a systemic periodic dose in the range of 0.001 mg to 1000 mg of compound per kilogram of **animal** body weight of a compound having the formula: ##STR7## wherein R.sub.1, is selected from the group consisting of ##STR8## in which R.sub.7, R.sub.8, R.sub.9, R.sub.10, R.sub.11, R.sub.12, R.sub.13, R.sub.14, R.sub.15, R.sub.16, and R.sub.17 are, the same or different, each a hydrogen atom, a halogen atom, a C.sub.1 -C.sub.4 alkoxy group, a C.sub.1 -C.sub.4 alkylthio group, a trifluoro methyl group or a nitro group; R.sub.18, R.sub.19, R.sub.20 and R.sub.21 are, the same or different, each a hydrogen atom or a methyl group, k is an integer of 0 to 1 and l is an integer of 0 to 3; R2 and R.sub.3 are, the same or different, each a hydrogen atom, a halogen atom or a methyl group; R.sub.4 is a halogen atom or a methyl group; R.sub.5 and R.sub.6 are, the same or different, each a hydrogen atom, a halogen atom, a C.sub.1 -C.sub.4 haloalkyl group or a C.sub.1 -C.sub.4 haloalkoxy group; X, Y and Z are, the same or different, each an oxygen atom, a sulfur atom or a methylene group, m is an integer of 0 to 4, and n is an integer of 0 to 2, the dose being sufficient to supply an ovicidally effective amount of the selected compound to the ectoparasite when the ectoparasite feeds on the **animal**'s blood through out the dosage period.

5. A method according to claim 1 wherein the compound is administered to the **animal** host at a dose level of from about 0.1 mg/kg of **animal** body weight to about 200 mg/kg of **animal** body weight.

6. A method according to claim 1 wherein the compound is administered to the **animal** host at a dose level of from about 0.2 mg/kg of **animal** body weight to about 50 mg/kg of **animal** body weight.

7. The method of claim 1 wherein the ectoparasite is a flea and the warm blooded **animal** is either a dog or a cat.

8. The method of claim 4 wherein the ectoparasite is a flea and the warm blooded **animal** is either a dog or a cat.

13. A method according to claim 1 wherein a second systemic parasite control compound is administered selected from the group consisting of **avermectin**, **avermectin** derivatives, **milbemycin**, **milbemycin** derivatives, ivermectin, ivermectin derivatives, **milbemycin** oxime, **milbemycin** oxime derivatives, moxidectin, and moxidectin derivatives, or mixtures thereof.

21. The method of claim 1 wherein the dose is administered by an **implant**.

22. The method of claim 13 wherein the dose is administered by an **implant**.

23. The method of claim 21 wherein the **implant** is a composition comprising 6 parts elastomeric silicone and 1 part hydrophilic methacrylate polymer.

24. The method of claim 22 wherein the **implant** is a composition comprising 6 parts elastomeric silicone and 1 part hydrophilic methacrylate polymer.

25. A method of systemically controlling ectoparasites and endoparasites in warm blooded **animals** which comprises administering a single dose in the range of about 10 to 200 mg/kg of 2-[1-methyl-2-(-4-phenoxyphenoxy)ethoxy]pyridine (pyriproxifen) formulated to deliver an ovicidally effective amount to the **animals** blood stream for at least 25 days and 0.5 mcg/kg to 100 mg/kg of a parasite control compound selected from the group consisting of **milbemycin**, **milbemycin** derivatives, ivermectin, ivermectin derivatives, **milbemycin** oxime, **milbemycin** oxime derivatives, moxidectin, moxidectin derivatives, **avermectin**, and **avermectin** derivatives, or mixtures thereof, to a warm blooded **animal** such that ectoparasites feeding on the blood of the **animal** receive an ovicidally effective amount of pyriproxifen for at least 25 days.

26. The method of claim 25 wherein pyriproxifen is administered by an **implant**.

27. The method of claim 25 wherein both pyriproxifen and the selected parasite control compound are administered by **implant**.

28. The method of claim 25 wherein the ectoparasite is a flea and the warm blooded **animal** is either a dog or a cat.

33. A method according to claim 32 wherein the nutrient blood is dosed with pyriproxifen by administration of a dose of pyriproxifen to the host **animal** in the range of 0.001 to 1000 mg/kg of host **animal** body weight.

36. A method according to claim 33 wherein the dose is administered to the host **animal** orally.

37. A method according to claim 33 wherein the dose is delivered by an

implant.

IT **51570-36-6**, Milbemycin **51570-36-6D**, Milbemycin, derivs.
70288-86-7, Ivermectin 70288-86-7D, Ivermectin, derivs.
73989-17-0, Avermectin **73989-17-0D**, Avermectin, derivs.
113507-06-5, Moxidectin 113507-06-5D, Moxidectin, derivs.
129496-10-2, Milbemycin oxime 129496-10-2D, Milbemycin oxime, derivs.
(systemic ectoparasiticides contg. heterocyclic compd. and)

L60 ANSWER 6 OF 8 USPATFULL
AN 95:38452 USPATFULL
TI Slow release syneresing polymeric drug delivery device
IN Hsu, Terry T., North Wales, PA, United States
Michaels, Alan S., Chestnut Hill, MA, United States
PA Merck & Co., Inc., Rahway, NJ, United States (U.S. corporation)
PI US 5411737 19950502
AI US 1991-776913 19911015 (7)
DT Utility
FS Granted
EXNAM Primary Examiner: Page, Thurman K.; Assistant Examiner: Levy, Neil
LREP Rose, David L., DiPrima, Joseph F.
CLMN Number of Claims: 27
ECL Exemplary Claim: 1
DRWN 9 Drawing Figure(s); 4 Drawing Page(s)
LN.CNT 854
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB There is disclosed a slow release drug delivery device for the prolonged administration of topically active medicines which consists of a vehicle in which water is soluble and in which is dissolved the topically active drug which is formed into a stable organogel with a polymer matrix with a very low water absorbing capability. The organogel, in the presence of water or atmospheric water vapor, slowly imbibes such water into the vehicle and by doing so the vehicle becomes incompatible with the matrix and is slowly expelled therefrom. The vehicle dissolves the drug and the vehicle/drug combination is slowly pumped out of the polymeric matrix with substantially linear drug delivery occurring for periods in excess of 6 months. The drug delivery device may be used to administer drugs topically, as a collar or trans dermal patch, orally, as a slow delivery device, particularly as a ruminal bolus, or as a suppository or a subcutaneous **implant**. The preferred form for the drug delivery device is as a flea and tick collar for household pets and the preferred active drug is selected from the **avermectin** and **milbemycin** families of active antiparasitic agents.
AB There is disclosed a slow release drug delivery device for the prolonged administration of topically active medicines which consists of a vehicle in which water is soluble and in which is dissolved the topically active

drug which is formed into a stable organogel with a polymer matrix with a very low water absorbing capability. The organogel, in the presence of water or atmospheric water vapor, slowly imbibes such water into the vehicle and by doing so the vehicle becomes incompatible with the matrix and is slowly expelled therefrom. The vehicle dissolves the drug and the vehicle/drug combination is slowly pumped out of the polymeric matrix with substantially linear drug delivery occurring for periods in excess of 6 months. The drug delivery device may be used to administer drugs topically, as a collar or trans dermal patch, orally, as a slow delivery device, particularly as a ruminal bolus, or as a suppository or a subcutaneous **implant**. The preferred form for the drug delivery device is as a flea and tick collar for household pets and the preferred active drug is selected from the **avermectin** and **milbemycin** families of active antiparasitic agents.

CLM What is claimed is:
15. The drug delivery device of claim 1 where the drug is an **avermectin** or a **milbemycin**.

IT **51570-36-6**, Milbemycin 70288-86-7, Ivermectin
73989-17-0, Avermectin 149029-86-7
(flea and tick collar for pets contg., polymeric matrix for)

L60 ANSWER 7 OF 8 USPATFULL
AN 90:27931 USPATFULL
TI Parasiticidal **avermectin** derivatives
IN Roben, Wolfgang, Bergisch Gladbach, Germany, Federal Republic of
Stendel Wilhelm, Wuppertal, Germany, Federal Republic of
Andrews, Peter, Wuppertal, Germany, Federal Republic of
PA Bayer Aktiengesellschaft, Leverkusen, Germany, Federal Republic of (non-U.S. corporation)
PI US 4916120 19900410
AI US 1988-230221 19880801 (7)
PRAI DE 1987-3727648 19870819
DT Utility
FS Granted
EXNAM Primary Examiner: Brown, Johnnie R.; Assistant Examiner: Peselev, Elli
LREP Sprung Horn Kramer & Woods
CLMN Number of Claims: 7
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 430
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Parasiticidally active **avermectin** derivatives of the formula ##STR1## in which R.sup.1 stands for hydrogen, OH, C.sub.1-5 -alkanoyloxy, .alpha.-L-oleandrosyloxy, .alpha.-L-oleandrosyl-.alpha.-L-oleandrosyloxy, 4'-C.sub.1-5 -alkanoyl-.alpha.-oleandrosyloxy or 4"-C.sub.1-5 -alkanoyl-.alpha.-L-oleandrosyl-.alpha.-L-oleandrosyloxy,

R.sup.2 stands for hydrogen, OH, C.sub.1-5 -alkanoyloxy, or R.sup.2 stands for hydrogen when there is a double bond between C22 and C23,

R.sup.3 stands for straight-chain or branched alkyl or alkenyl, and

R.sup.4 stands for hydrogen, OH, C.sub.1-5 -alkanoyloxy, heterocyclylcarbonyloxy, or the bond between the C atoms C22 and C23 is a single or a double bond and the double bond of the cyclohexene ring can be between the C atoms C3 and C4 or between the C atoms C4 and C5.

TI Parasiticidal **avermectin** derivatives

AB Parasiticidally active **avermectin** derivatives of the formula ##STR1## in which R.sup.1 stands for hydrogen, OH, C.sub.1-5 -alkanoyloxy, .alpha.-L-oleandrosyloxy, .alpha.-L-oleandrosyl-.alpha.-L-oleandrosyloxy, 4'-C.sub.1-5 -alkanoyl-.alpha.-oleandrosyloxy or 4"-C.sub.1-5 -alkanoyl-.alpha.-L-oleandrosyl-.alpha.-L-oleandrosyloxy,

SUMM Enteral administrationn of the active compounds occurs, for example, orally in the form of powders, tablets, capsules, pastes, boli, drinks, granules, orally applicable solutions, suspensions or emulsions, or medicated feed or drinking water. Dermal administration occurs, for example, in the form of dipping, spraying or pouring on and spotting on and powdering. Parenteral administration occurs, for example, in the form of injections (for example intramuscular, subcutaneous or intravenous) or by **implants**.

SUMM It can also be advantageous to administer the active compounds in formulations which retard the release of the active compound. Those which may be mentioned are moulded articles containing the active compound such as, for example, sheets, bands, strips, neckbands, **ear** tags, tail marks, limb bands, halters and marking devices. **Implants** and boli containing the active compound may also be mentioned.

CLM What is claimed is:

1. An **avermectin** derivative of the formula ##STR8## in which R.sup.1 stands for hydrogen, OH, C.sub.1-5 -alkanoyloxy, .alpha.-L-oleandrosyloxy, .alpha.-L-oleandrosyl-.alpha.-L-oleandrosyloxy, 4'-C.sub.1-5 -alkanoyl-.alpha.-L-oleandrosyloxy or 4"-C.sub.1-5 -alkanoyl-.alpha.-L-oleandrosyl-.alpha.-L-oleandrosyloxy, R.sup.2 stands for hydrogen, OH, C.sub.1-5 -alkanoyloxy, or R.sup.2 stands for hydrogen when there is a double bond between C22 and C23, R.sup.3 stands for straight-chain or branched C.sub.1-4 -alkyl or C.sub.2-8 -alkenyl, R.sup.4 stands for hydrogen, OH, C.sub.1-5 -alkanoyloxy, or the bond between the C atoms C22 and C23 is a single or a double bond and the double bond of the cyclohexene ring can be between the C atoms C3 and 4 or between the C atoms C4 and C5, and X stands for hydrogen or halogen.

6. A method of combating parasites which comprises applying to such parasites or to an **animal** habitat for such parasite a parasiticidally effective amount of a compound according to claim 2.

L60 ANSWER 8 OF 8 USPATFULL

AN 89:56392 USPATFULL

TI Treatment for fescue toxicosis in grazing animals

IN Wallace, Dennis H., Columbia, MO, United States

PA Merck & Co., Inc., Rahway, NJ, United States (U.S. corporation)

PI US 4847243 19890711
AI US 1987-105837 19871008 (7)
DT Utility
FS Granted
EXNAM Primary Examiner: Yarbrough, Amelia Burgess
LREP Rose, David L., Sudol, Michael C.
CLMN Number of Claims: 11
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 263
AB There is disclosed a method for the prevention of fescue toxicosis in grazing animals. Fescue toxicosis results from a grazing animal ingesting certain toxins present in or on the grass which can impair growth, reproductive performance, and is sometimes fatal. It has been discovered that the administration of ivermectin or related **avermectin** compounds is effective in reducing or eliminating the toxic effects of fescue endophyte ingestion.
AB There is disclosed a method for the prevention of fescue toxicosis in grazing animals. Fescue toxicosis results from a grazing animal ingesting certain toxins present in or on the grass which can impair growth, reproductive performance, and is sometimes fatal. It has been discovered that the administration of ivermectin or related **avermectin** compounds is effective in reducing or eliminating the toxic effects of fescue endophyte ingestion.
CLM What is claimed is:
1. A method for treating the symptoms of fescue toxicosis in animals ingesting tall fescue infected with an endophytic fungus which comprises
administering to such animals an effective amount of an **avermectin** or a **milbemycin** compound.

11. The method of claim 10 wherein the active compound is administered as a subcutaneous **implant**.